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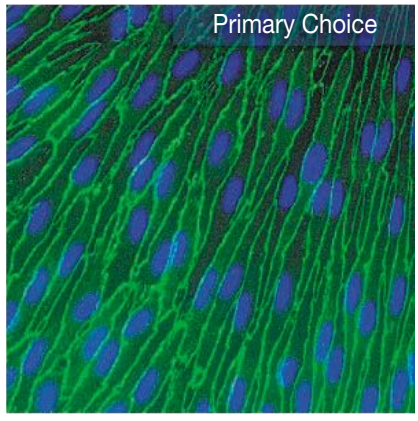

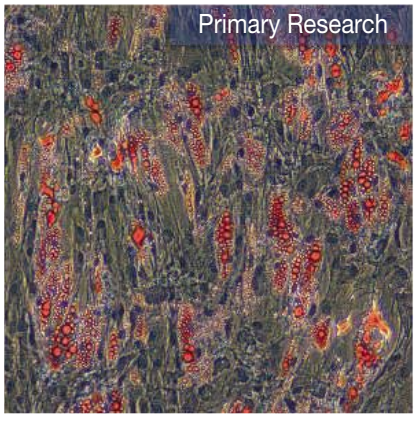

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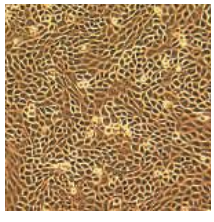

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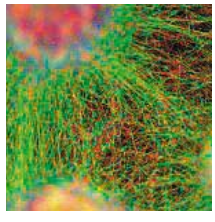

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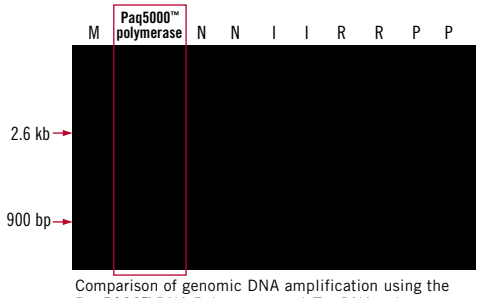

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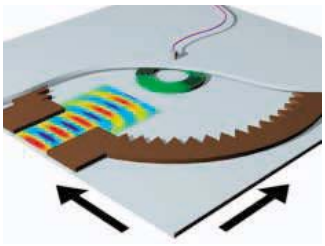

SCIENCE EXPRESS

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GENETICS

HTRA1 Promoter Polymorphism in Wet Age-Related Macular Degeneration
A. DeWan et al.
10.1126/science.1133807

A Variant of the *HTRA1* Gene Increases Susceptibility to Age-Related Macular Degeneration
Z. Yang et al.
People who have one of the normal variants of a protein-degrading enzyme are at increased risk of developing an aggressive form of age-related macular degeneration.
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D. Schurig et al.
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Recent Greenland Ice Mass Loss by Drainage System from Satellite Gravity Observations
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PERSPECTIVE: How Fast Are the Ice Sheets Melting?
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Response to Comment on "Stability via Asynchrony in *Drosophila* Metapopulations with Low Migration Rates"
S. Dey and A. Joshi
full text at www.sciencemag.org/cgi/content/full/314/5798/420b

BREVIA

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Exposure to Scientific Theories Affects Women's Math Performance
I. Dar-Nimrod and S. J. Heine
Ascribing gender differences in performance on math tests to genetics adversely affects girls' scores on subsequent tests, but ascribing such differences to experience does not.

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T. Brun, I. Devetak, M.-H. Hsieh
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>> Perspective p. 427

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Anisotropy and Corotation of Galactic Cosmic Rays
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>> Perspective p. 429

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G. Sansone et al.
Single-cycle 130-attosecond light pulses, useful for probing electron dynamics, can be generated by modulating the polarization state of 5-femtosecond pulses in argon.

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Molecular Imaging Using a Targeted Magnetic Resonance Hyperpolarized Biosensor
L. Schröder, T. J. Lowery, C. Hilty, D. E. Wemmer, A. Pines
Magnetic resonance images of a single biomolecule can be obtained from the amplified signal of a bound xenon probe that exchanges with surrounding bulk xenon.
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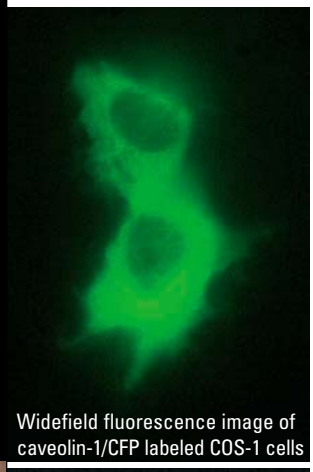
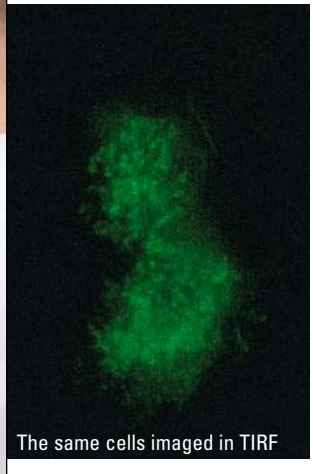


Widefield fluorescence image of caveolin-1/CFP labeled COS-1 cells



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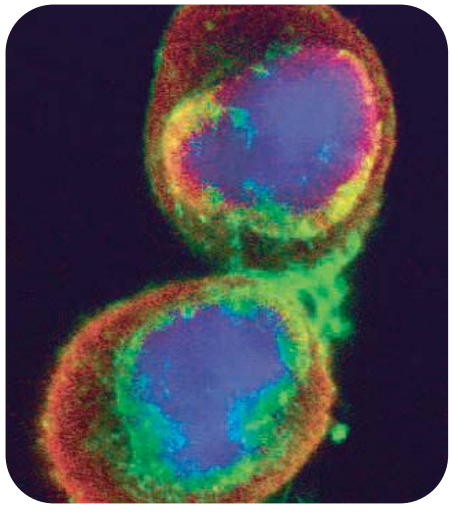

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SCIENCE (ISSN 0036-8075) is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue, NW, Washington, DC 20005. Periodicals Mail postage (publication No. 484460) paid at Washington, DC, and additional mailing offices. Domestic individual membership and subscription (51 issues): $139 ($74 allocated to subscription). Domestic institutional subscription (51 issues): $650; Foreign postage extra: Mexico, Caribbean (surface mail) $55; other countries (air assist delivery) $85. First class, airmail, student, and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. Publications Mail Agreement Number 1069624. **Printed in the U.S.A.**

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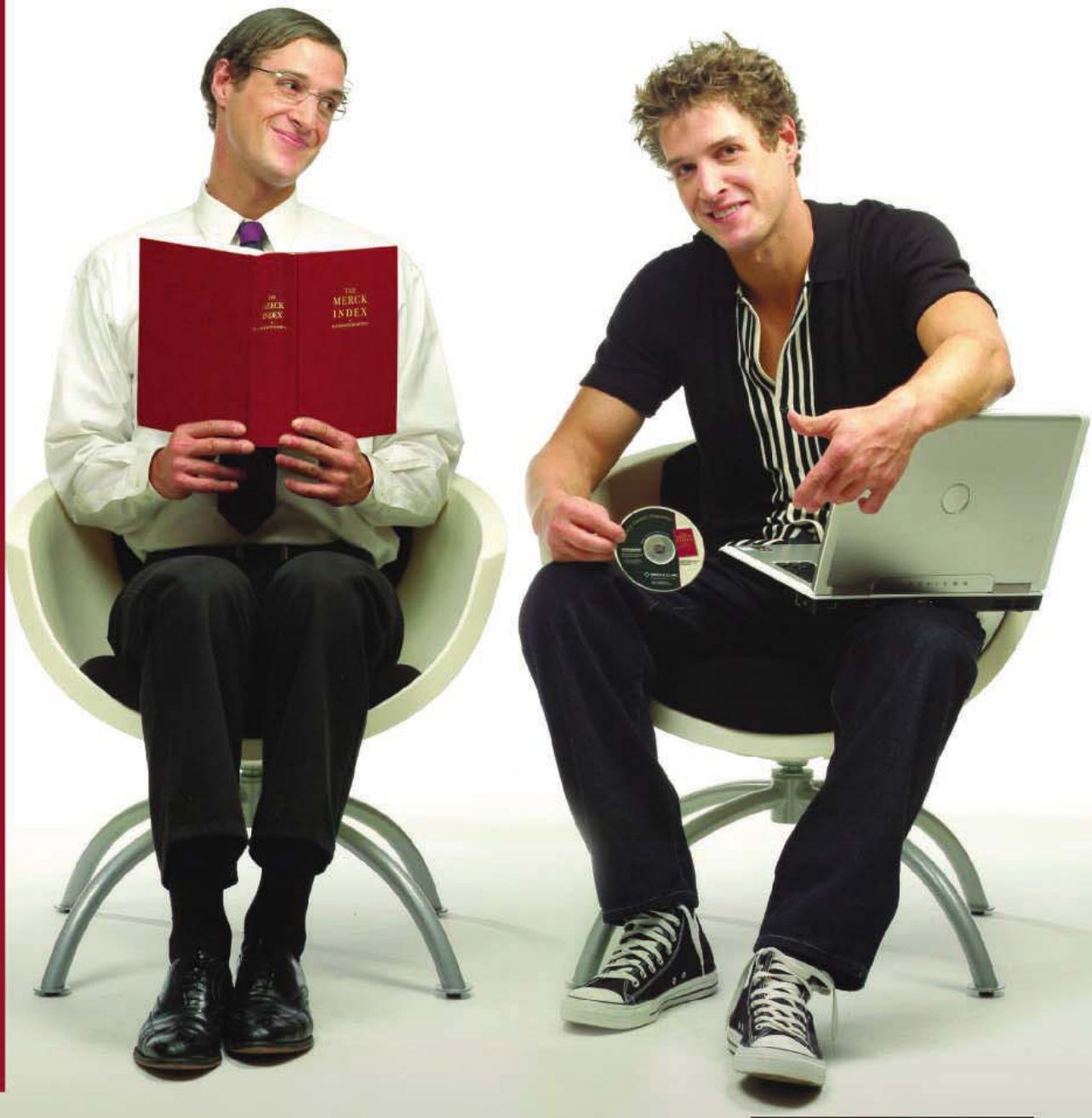

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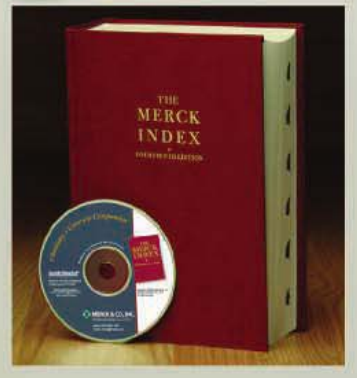

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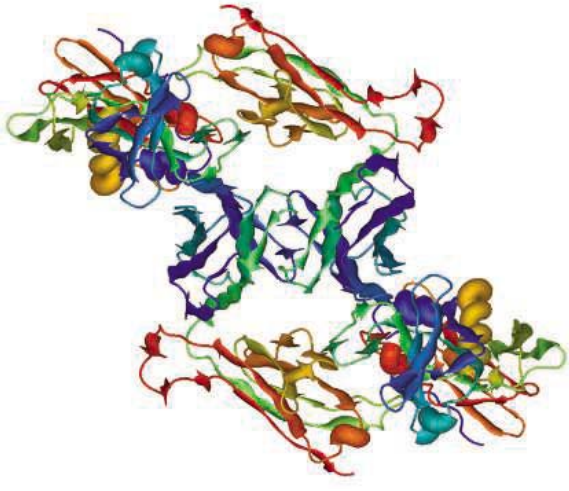

Crystal structure of a superantigen and T cell receptor.

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PERSPECTIVE: Caspase Inhibitors Promote Alternative Cell Death Pathways
P. Vandenabeele, T. Vanden Berghe, N. Festjens
In the absence of apoptosis, cells may undergo autophagic or necrotic cell death.

PERSPECTIVE: Superantigens—Supersignalers?
R. Zamoyska
Superantigens activate an alternative pathway during T cell activation that involves $G\alpha_{11}$ of the Gq family and PLC-β signaling.

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www.sciencecareers.org CAREER RESOURCES FOR SCIENTISTS

GLOBAL: Mastering Your Ph.D.—Giving Great Presentations
P. Gosling and B. Noordam
Speaking in front of a group of people, our newest columnists write, doesn't have to be an unnerving experience.

US: Tooling Up—Traits of the Key Players
D. Jensen
Dave Jensen reviews the qualities scientists must have to be key players in an industrial setting.

US: Working at the National Labs—Fermilab
A. Fazekas
High-energy physics researchers share their thoughts about working at the Fermi National Accelerator Laboratory.

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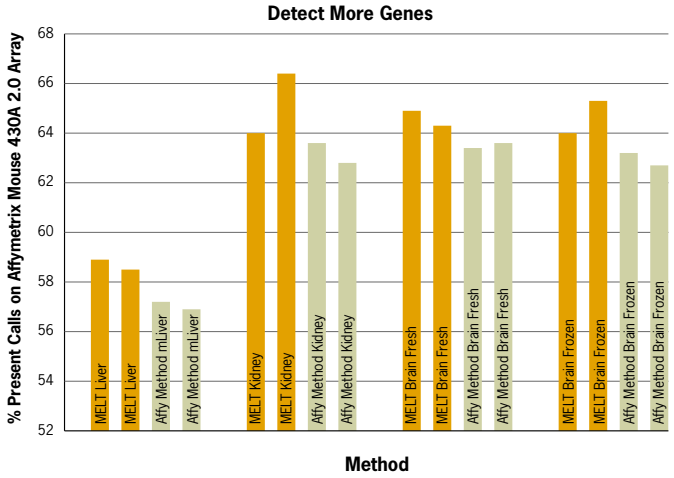

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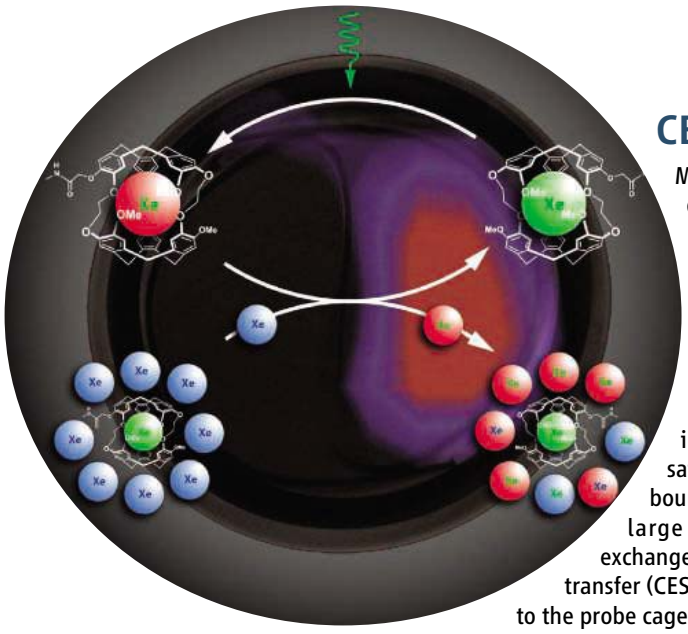

CEST with Zest

Magnetic resonance imaging of biological systems generally detects local concentration gradients of highly abundant compounds, such as water. Various molecular probes can be used to target more specific regions or substrates for imaging, but often at the expense of greatly reduced sensitivity. **Schröder *et al.*** (p. 446; see the Perspective by **Driehuys**) combine two techniques to achieve a large measure of both specificity and sensitivity. They prepare a molecular cage framework that can encapsulate hyperpolarized xenon (Xe) in close proximity to a selectively bound target. To compensate for the relatively low probe concentration, they detect the bound Xe through its modulation of the signal arising from the large pool of unbound Xe as the bound and unbound atoms exchange positions—a method termed chemical exchange saturation transfer (CEST). The authors demonstrate the method by appending biotin to the probe cage and selectively imaging an in vitro avidin sample.

Entangled Quantum Error–Correction

Quantum error–correction codes were introduced just over a decade ago to tackle the problem of decoherence, which at the time was thought to be an insurmountable obstacle to the development of quantum information processing. The present quantum error–correction codes are effective but somewhat limited in application and tend to be slow. **Brun *et al.*** (p. 436, published online 28 September; see the Perspective by **Gottesman**) present a theory of entanglement-assisted quantum error correction, a technique that generalizes and simplifies the existing theory of stabilizer codes and opens the possibility of whole new classes of highly efficient codes to protect quantum information from decoherence. The existing classes of quantum error–correcting codes can now be seen to be special cases of a much larger class, the entanglement-assisted error-correcting codes.

In a Big Spin

One way in which the particles that become cosmic rays can obtain their high energy is through acceleration by shock waves, such as those produced by supernovas, including nearby ones within our own Galaxy. However, the paths that cosmic rays take are then scrambled by interstellar magnetic fields, which obscures their origin. **Amenomori *et al.*** (p. 439; see the Perspective by **Duldig**) have mapped the distribution of cosmic rays on the sky using 16 years of data from the Tibet Air Shower Array. They see clear anisotropies, including a component associated with the Cygnus spiral arm of the Milky Way. Although present at energies up to tens of tera-electron volts (TeV), the anisotropic spots disappear at an energy near 300 TeV. This result suggests that the spots arise through the galactic rather than heliospheric magnetic field, and corotate with the gas and stars in the Milky Way.

Single-Cycle Attosecond Pulses

The availability of single-cycle isolated attosecond pulses provides the possibility of probing ultrafast electron dynamics in atoms and molecules where the strong-field processes are driven by the electric field of the attosecond pulses, rather than by the brute-force response to their high intensity. **Sansone *et al.*** (p. 443) have now generated isolated, single-cycle 130-attosecond pulses with energies in the extreme ultraviolet (~ 36 electron volts). Phase-stabilized, 5-femtosecond infrared driving pulses with modulated-polarization state were fired into an argon-filled gas cell to generate these higher harmonics.

Cloudy Future

Rising concentrations of atmospheric CO_2 will have two main impacts, those of global warming and acidification of the oceans. It is unclear whether anthropogenic CO_2 emissions can be reduced quickly enough to avoid potentially damaging consequences, and one alternative is that we "geo-engineer" climate in order to mitigate some of the damaging effects of atmospheric CO_2 buildup. **Wigley** (p. 452, published online 14 September; see the news story by **Kerr**) explores one option—injecting sulfate aerosol precursors into the stratosphere, which would increase the number of aerosol particles that can function as cloud condensation nuclei and increase cloud coverage, as is the case after large volcanic eruptions like that of Mount Pinatubo in 1991. The net effect would be to reflect more sunlight back into space, but this approach would have no positive influence on ocean acidification.

Winds, Water, and Wetlands

Wetlands along the coast of the Gulf of Mexico help protect inland areas from storm-driven ocean surges, and the effects of their erosion became painfully clear after Hurricanes Katrina and Rita made landfall in 2005. Coastal wetlands have been thought to gain and maintain mass through the sediment deposits that occur when rivers overflow during flooding events. **Turner *et al.*** (p. 449, published online 21 September) show that the deposition of sediments by hurricanes is actually

Continued on page 383

CREDITS (TOP TO BOTTOM): SCHRÖDER *ET AL.*; TURNER *ET AL.*

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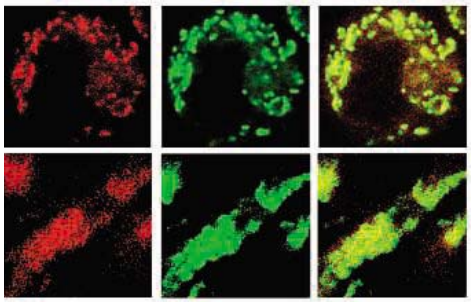
the dominant process. This finding should have considerable impact on the implementation of wetland restoration projects in the region.

Viral Host Exploitation

Human immunodeficiency virus type–1 (HIV-1) is a retrovirus and uses reverse transcription to generate DNA, which enters the nucleus to integrate with the host DNA. The latter process is catalyzed by a virally–encoded integrase enzyme, and this latent reservoir represents a major obstacle to the treatment of HIV disease. The transcriptional coactivator LEDGF/p75 (p75) binds the HIV-1 integrase protein and protects it from degradation by the cell's proteasomal machinery. **Llano *et al.*** (p. 461, published online 7 September) now show that p75 plays a crucial role in viral integration by acting as tether between the integrase and chromatin. For the case of baculovirus replication, **Goley *et al.*** (p. 464) now find this process requires the redistribution of the actin cytoskeleton into the nucleus of infected cells. *Autographa californica* induces nuclear actin assembly by recruiting the host actin-nucleating Arp2/3 complex into the nucleus and activating it with p78/83, a Wiskott-Aldrich syndrome (WASP)–like viral protein. This unanticipated role for the assembly of actin in the nucleus may play a role in the action of other pathogens.

Protein Degradation and Growth Regulation

Controlled protein degradation is a fundamentally important cellular regulatory mechanism. **Dorrello *et al.*** (p. 467; see the Perspective by **Sonenberg and Pause**) searched for binding partners of the ubiquitin ligase $SCF^{\beta TRCP}$ and detected programmed cell death protein 4 (PDCD4). The growth factor–stimulated protein kinase, S6K1, phosphorylated PDCD4 and promoted its ubiquitination by $SCF^{\beta TRCP}$ and consequent degradation. The degradation of PDCD4 relieved its inhibitory effect of on a translation initiation factor and enhanced protein synthesis. Thus, regulated destruction of PDCD4 appears to regulate cell proliferation and cell size.



CREDIT: MAHATA *ET AL.*

Fixing Faulty Mitochondria

Mitochondrial dysfunction plays a key role in the etiology of many complex human diseases as well as aging. Disease-causing mitochondrial transfer RNA (tRNA) mutations are targets for the development of potential therapeutic strategies. **Mahata *et al.*** (p. 471) now find that the efficient tRNA import apparatus found in protozoan parasite *Leishmania* can be used to induce the import of a complementing cytosolic tRNA into human mitochondria and can rescue mitochondrial function in mutant cells.

Genetic Contribution to Memory

Human memory is a polygenic trait. **Papassotiropoulos *et al.*** (p. 475) analyzed a genome-wide panel of more than 500,000 genetic polymorphisms for association with performance on memory tests in a group of Swiss subjects. An association was found in a polymorphism within a neuronal protein called KIBRA, which has been implicated in synaptic function. The association was also present in a group from the United States and a second group from Switzerland. KIBRA is expressed in areas of the brain that control memory, and brain activity during memory retrieval is correlated with the KIBRA allele.

Living Deep in the Sunless Sea

A sulfate-reducing bacterium has been isolated from a seam of water that was found by drilling in a gold mine at a depth of 2.8 kilometers. The microbes appear to have survived for tens of millions of years on geological hydrogen and sulfate sources without any nutrients derived from photosynthesis. **Lin *et al.*** (p. 479) report on the chemical composition of the groundwater, its apparent microbiological composition, the geological and biological processes involved, and the rates at which such subsurface communities are sustained.

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David A. King is the Chief Scientific Adviser to H.M. Government and Head of the Office of Science and Innovation, London, SW1H 0ET. E-mail: mpst.king@dti.gsi.gov.uk

Aid to Enhance Africa's Skills

THE PAST 18 MONTHS HAVE BEEN IMPORTANT FOR AFRICA, WITH THE EMERGENCE OF A NEW vision for how to eliminate the country's poverty for good. Last year's Gleneagles G8 summit made unprecedented commitments to eliminating debt and providing levels of aid that could finally make a difference. In particular, both the Commission for Africa and Gleneagles emphasized science and technology as a central plank in this effort. Unfortunately, little attention has been paid to the need for highly trained scientists, engineers, medical practitioners, and agriculturalists as a developmental priority. This is a recipe for disappointment.

Simply bringing Western technology and dumping it in the middle of Africa is not the answer. I have recently been working with Brazil and several southern African countries to examine the potential transfer to Africa of Brazil's highly effective technology for converting sugarcane into fuel. Our recent analysis showed that key southern African countries could use this approach to revive their sugarcane industry and reduce oil imports by a factor of 2 by 2020. However, it will not work unless those same countries can produce the chemists and engineers to generate this new fuel, sustain its production, and distribute it.

And bringing Westerners in to remedy the shortage of African skills in science and engineering cannot be a long-term solution. Take access to hygenic water, which can revolutionize both life expectancy and the standard of living. Thanks to civil engineering projects, every citizen of a medium-sized city in the United Kingdom or the United States can drink clean water. But if you took enough UK or U.S. civil engineers to Africa to do that for one medium-sized city every week, fitting out the entire continent would take 20 years. No Western country could or should provide personnel on that scale, meaning that the engineers will have to come from Africa itself.

It may seem perverse to be worrying about how many scientists and engineers a country produces when adult literacy is so low. But we need to ensure that at least a proportion of people develop high-standard scientific and technological skills relevant to their home countries. This is not elitism. Even a relatively small number of people who are well-educated in science and technology can make a significant difference to their communities. The key will be partnerships under African leadership; for example, provided by the New Partnership for African Development; under the auspices of the African Union. Skill development has been a key objective at the behest of Africans, reflected in plans for networking and centers of excellence of the kind that have been successful in similar situations.

These realistic proposals require assurance that money will be in place to fulfill them. The trouble now is that foreign aid is both insufficient and wrongly directed. A major defect is that most aid to Africa is tied to the condition that it be spent using only the donor countries' contractors and companies. This self-serving rule weakens local decision-making and undermines prospects that the recipient country can follow its own strategy for growth. The British government has taken a bold lead in untying its development assistance. For example, in Botswana, the United Kingdom untied all its aid in 1998, stimulating strengthened growth under Botswana's own national leadership. In Rwanda, the United Kingdom untied £200 million of development assistance, which is helping to create a base for both general education and for scientifically and technologically trained Rwandans, allowing that shattered country to rebuild and then grow her economy.

I am an African. And when I look at where my home continent sits on the global map of life expectancies, I find it heartbreaking. Whereas modern technological benefits have brought high life expectancies to the rest of the world, for most of sub-Saharan Africa the figure is between 40 and 55. The continent of Africa is the greatest tragedy on Earth. We in the United Kingdom are working with governments around the world to reverse that tragedy. And we are calling especially on the United States and our other G8 partners to stand with us in this vital endeavor. Africa has her vision. What she needs now is the means.

– David A. King

10.1126/science.1133498

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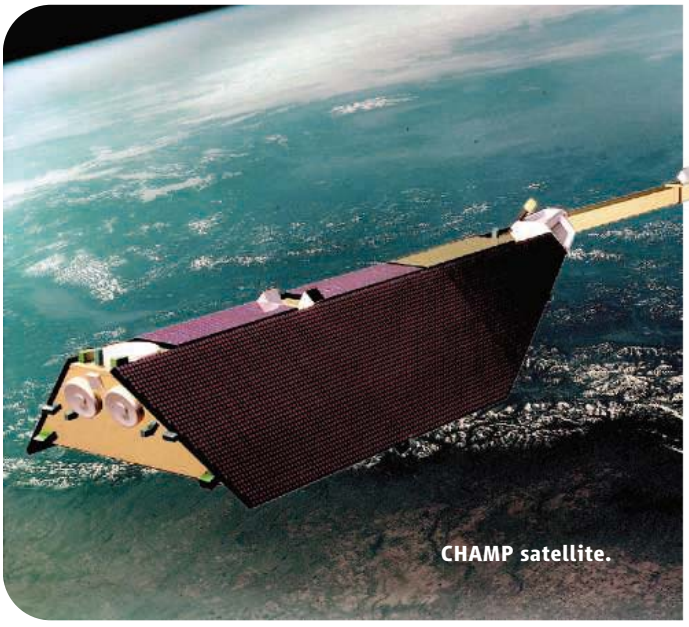


CHAMP satellite.

ASTROPHYSICS

Blast Wave Bounce

On 27 December 2004, a magnetic star, or magnetar, erupted. This event generated a huge burst of gamma rays that were spotted by gamma-ray and x-ray telescopes. In a fraction of a second, the magnetar SGR 1806-20 gave off as much energy as the Sun does in a quarter of a billion years. The energetic blast released by the star was sufficiently large for the generated gamma rays to affect Earth's environment when they arrived, causing ionosphere disturbances measured by radio receivers. Mandea and Balasis have found that currents set up in the ionosphere by the crashing gamma rays briefly upset Earth's magnetic field. The records of the CHAMP and DEMETER satellites contain a faint ringing signal of the magnetar's explosion with a period of 7.5 s for the duration of the flare. — JB

Geophys. J. Int., 10.1111/j.1365-246X.2006.03125.x (2006).

IMMUNOLOGY

Two Ways to Bug Worms

Innate immunity in the nematode worm *Caenorhabditis elegans* involves two genes: *PMK-1* and *DAF-16,* which is up-regulated by the insulin/insulin-like growth factor tyrosine kinase *DAF-2*. Worms carrying loss-of-function mutations in *pmk-1* are more sensitive to pathogens, whereas *daf-2* null mutants are more resistant. Troemel *et al*. have shown that the pathogen resistance observed in *daf-2* mutants requires a functional *PMK-1* gene and that *PMK-1* works either downstream or in parallel with *DAF-2*. However, the downstream targets of the two genes do not overlap. Detailed analyses of pathogen resistance suggest that *PMK-1*, unlike *DAF-16*, is specific to the immune response required for pathogen response, whereas the *DAF-2 DAF-16* pathway appears to play a less precise role in immunity. Thus, at least two separate pathways contribute to innate immunity in *C. elegans*. — LMZ

PloS Genet. **2**, 10.1371/journal.pgen.0020183.eor (2006).

BIOTECHNOLOGY

Multicultural Metabolic Map

The microbe-based treatment of wastewater has never been a glamorous topic of conversation, and efforts at improving the efficiency of solute removal have largely been empirical in approach. Furthermore, the population of microbes may, at times, fluctuate unpredictably, which can result in the collapse of the entire community. García Martín *et al.* attempt to define the genomic composition of the candidate species, referred to as *Accumulibacter phosphatis*, that acquires inorganic phosphate, sequesters it as polyphosphate, and then conveniently sinks to the bottom of the treatment tank. From two lab-scale samples of sludge (derived from wastewater plants in Wisconsin, USA, and Brisbane, Australia), they obtained enough sequence to estimate the genome size of *A. phosphatis* as 5.6 Mb, with a high degree of sequence identity between the two samples. The list of genes is consistent with an aerobic build-up of polyphosphate, which is then used as an energy source for the anaerobic caching of volatile organic acids as polyhydroxyalkanoates. An unexpected (inferred) capacity for nitrogen fixation and a parcel of cobalamin-dependent enzymes suggest that *A. phosphatis* might thrive in an environment supplemented with cobalt and low in fixed nitrogen. — GJC

A wastewater treatment plant.

Nat. Biotechnol. **24**, 1263 (2006).

CLIMATE SCIENCE

Time to Talk

Earth's climate is warming, and carbon dioxide emitted from the burning of fossil fuel is very likely to be the major cause. Global temperatures are projected to rise above preindustrial values by 1.5° to 5.8°C by the end of the 21st century. The search is on for ways to slow warming, potentially by large-scale climate geoengineering.

One possible approach to this risky endeavor is to inject sulfate precursors into the stratosphere (see Wigley, Reports, 20 October 2006, p. 452), because sulfate aerosols reflect sunlight and would have a consequent cooling effect. In an attempt to lay the foundation for a more thorough discussion of climate geoengineering options Crutzen discusses the theoretical basis, possible methodologies, and advantages and disadvantages of such a scheme. Five other authors (Cicerone, Kiehl, Bengtsson, MacCracken, and Lawrence) weigh in on the history of such proposals, the practical as well as ethical considerations of various approaches, and how best to evaluate different geoengineering schemes. The authors make it clear that geoengineering climate is a less desirable potential solution to warming than controlling greenhouse emissions, and that only if warming causes sufficiently harmful impacts would geoengineering be a better choice. — HJS

Clim. Change **77**, 211; 221; 227; 229; 235; 245 (2006).

Continued on page 389

CREDITS (TOP TO BOTTOM): GFZ POTSDAM; TRINA MCMAHON

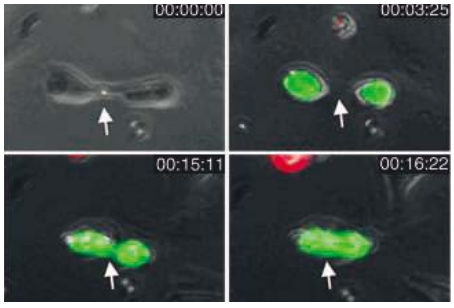
Continued from page 387

MICROBIOLOGY

Opportunistic Invasion

Pseudomonas aeruginosa is a ubiquitous opportunistic pathogen that cannot infect healthy humans unless there is a preexisting injury to the epithelium. Shafikhani and Engel describe how *P. aeruginosa* capitalizes on epithelial wounds to establish itself within the host by using multiple strategies to prevent wound healing. The pathogen injects a protein termed exotoxin T (ExoT) into the cytosol of target cells using a specialized type III secretion apparatus. Once inside the target host cells, ExoT inhibits cytokinesis: the process by which daughter cells are physically separated during cell division. Two domains of ExoT, an N-terminal GTPase-activating domain and a C-terminal ADP-ribosyl transferase domain, appear to act redundantly, one blocking an early step of cytokinesis, the other blocking a later step. This blocking of cytokinesis prevents further cell proliferation and thus helps to prevent the efficient closure of wounds, allowing access to further bacteria, which can go on to establish an acute infection. — SMH

Proc. Natl. Acad. Sci. U.S.A. **103**, 15605 (2006).



Cells containing ExoT (green) complete mitosis but fail to complete cytokinesis.

CREDIT: SHAFIKHANI AND ENGEL, *PROC. NATL. ACAD. SCI. U.S.A.* **103**, 15605 (2006)

COMPUTER SCIENCE

From Birds to Boards

One way to simulate a complex phenomenon such as the flocking of birds is to build a detailed computer model that incorporates the motion of all individuals as well as rules for their interaction. Many aspects of the underlying mechanisms must be incorporated into the program from the start, and such a system could be susceptible to wildly nonlinear outcomes. An alternative is to build a large number of autonomous entities having no central controller, and then allow the collective behavior to emerge over time through trial and error. As Liu and Tsui explain, such computing models have been labeled "nature-inspired" because they are truly analogous to the way birds flock or ants in a colony engage in purposeful collective behavior. The basic entities in such a model (which could be either software modules or actual hardware robots with internal software) are self-organized, most strongly influenced by local interactions, and capable of adapting their behavior in response to a changing environment. These emergent adaptive computing systems may find applications in studies of such complex collections of interacting entities as the human immune system, economic markets, or ecological communities. — DV

Commun. ACM **49**, 59 (2006).

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<< XIAP As a Positive Feedback Regulator of Capase Activation

Inhibitor of apoptosis proteins (IAPs) are best known for their roles as inhibitors of caspases and thus of apoptotic cell death. Legewie *et al.* develop a mathematical model of the core intrinsic apoptotic process involving Apaf-1, caspase 9, caspase 3, and X-linked IAP (XIAP). In the wild-type model, as active Apaf-1 concentration increased, the time course with which active caspase 3 was produced decreased as expected. When the activation of caspase 3 was plotted against the concentration of active Apaf-1, a bistable and irreversible state was observed both in the wild-type model and in a caspase 9 mutant model. This suggested that the positive feedback between caspase 9 and caspase 3 was not the only contributor to bistability in the system. Further analysis suggested that XIAP contributed a positive feedback to caspase 3 activation. Caspase 3 was proposed to sequester XIAP away from caspase 9 under conditions of strong stimulation, thereby allowing caspase 9 to become further activated and ultimately allowing caspase 3 to be activated. The bistability and irreversibility of the models depended on the concentrations of both caspase 3 and caspase 9, with only the wild-type model showing irreversibility in the physiological concentrations of each caspase, indicating that both caspase 3–mediated feedback and XIAP-mediated feedback contribute to irreversible bistability under physiological conditions. The models echo observed differences in cellular responses to apoptotic stimuli by showing that the all-or-none threshold of the system is influenced by the abundance of caspase 3, caspase 9, and XIAP. — NRG

PLoS Comput. Biol. **2**, e120 (2006).

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Information for Contributors

See pages 102 and 103 of the 6 January 2006 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

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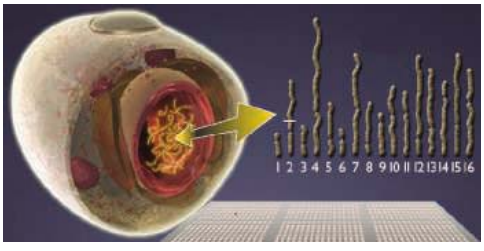
EDUCATION

Learning to Read the Dots

Undergraduates can get up to speed on gene chips with the Microarrays MediaBook, a snazzy animated tutorial hosted by biology professor A. Malcolm Campbell of Davidson College in North Carolina. Using the example of yeast cells growing with and without oxygen (below), the site leads readers through the basics of making and interpreting microarrays. Students can then dig deeper into techniques for analyzing results. They can learn about hierarchical clustering to identify genes that might work together and the significance of fold changes, the alteration in gene activity compared with controls. >> gcat.davidson.edu/Pirelli/index.htm



LINKS

Bioinformatics Home Base

Biologists who lament, "So many databases, so little time," should check out this portal from the University of Pittsburgh in Pennsylvania. The site provides brief descriptions of more than 1500 free bioinformatics databases and tools in categories such as immunology, genomics, and RNA. If you're looking for data on how pathogens alter gene activity in immune cells, for instance, follow the link to the Macrophage Expression Atlas in the U.K. Or the site can help you sift through the more than 70 databases with information on plant genes and proteins. >> www.hsls.pitt.edu/guides/genetics/obrc

RESOURCES

Earth Science Defined

If you think that teleconnection has something to do with phone calls or don't know that SCA stands for "snow-covered area," visit this collection of earth science references from NASA.* The site corrals more than 50 glossaries for fields from fisheries to remote sensing. Browsing the meteorology offerings will reveal that "teleconnection" refers to the correlation between weather patterns in distant parts of the world. There's also a list of sites that spell out acronyms and abbreviations. Among the glossaries at this smaller collection from the National Oceanic and Atmospheric Administration† are two pages on El Niño lingo. >>

* gcmd.gsfc.nasa.gov/Resources/FAQs/acronyms.html
† www.cdc.noaa.gov/ClimateInfo/tools.html

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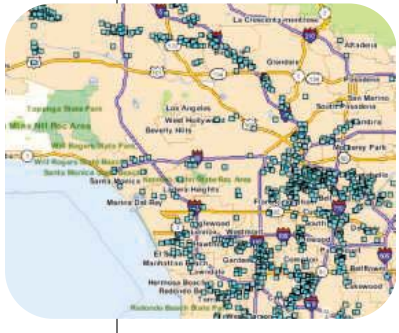
CREDITS (TOP TO BOTTOM): AMERICAN CHEMICAL SOCIETY; A. MALCOLM CAMPBELL; EPA

EXHIBITS

STROLL THROUGH CHEMISTRY HISTORY

Gerty and Carl Cori (above) shared more than most married couples, including a lab, a fascination with carbohydrate metabolism, and the 1947 Nobel Prize in physiology or medicine. The pair revealed how the body adjusts its sugar supply by breaking down and rebuilding glycogen. Their work is one of the milestones showcased at The National Historic Chemical Landmarks Web site. The 5-year-old exhibit from the American Chemical Society in Washington, D.C., explores more than 30 firsts in medicine, industry, consumer products, and basic science, adding a few new examples each year. You can also check out locales where revolutions in chemical research or production occurred, such as the Savannah Pulp and Paper Laboratory in Georgia and the Polymer Research Institute in New York City, which helped spark an explosion of interest in the giant molecules. >> center.acs.org/landmarks/index.html

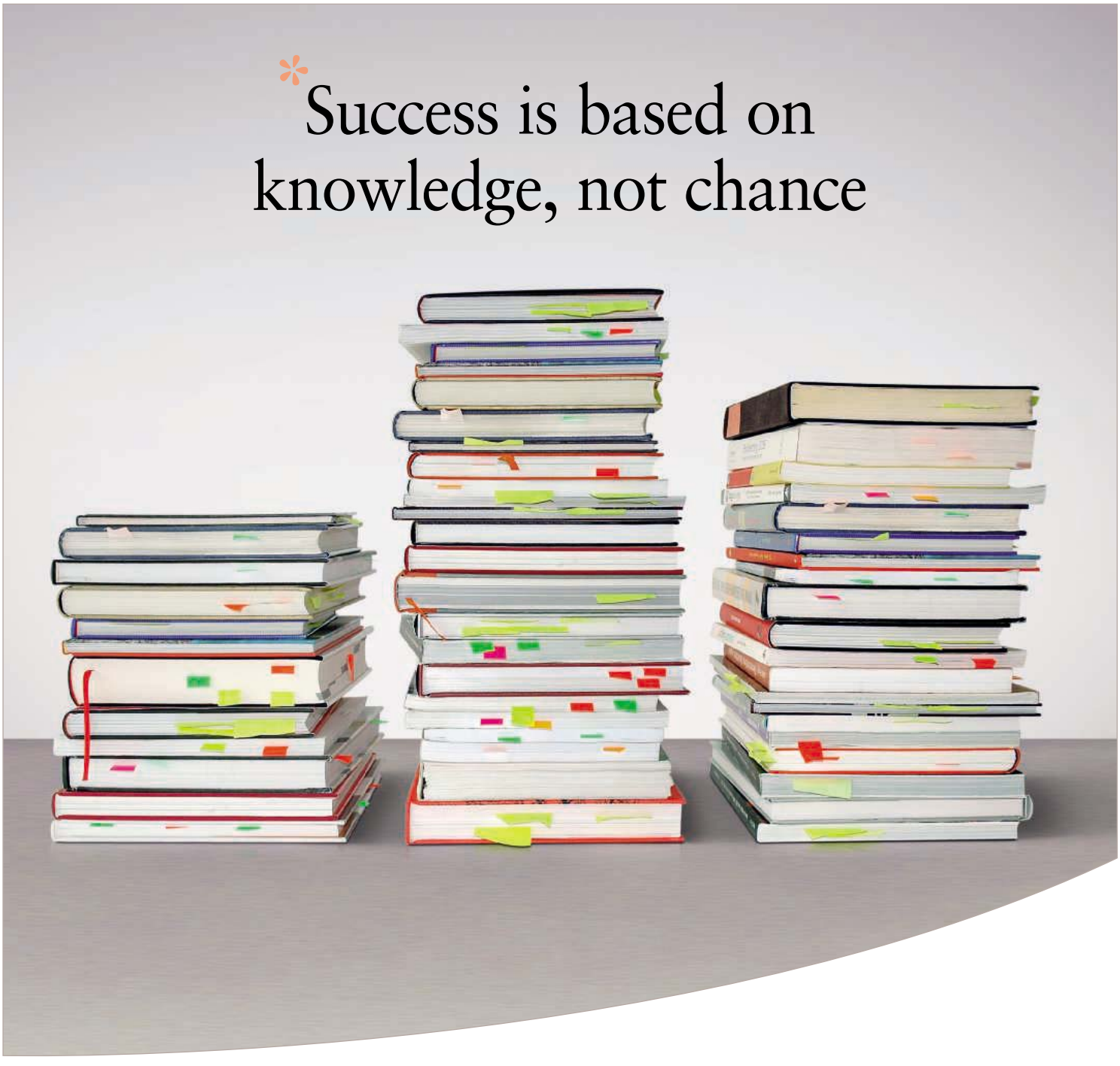


TOOLS

<< Follow That Smoke

Los Angeles is infamous for throngs of polluting cars, but electronics plants and other facilities that spew toxic compounds also clutter the area (turquoise squares at left). To track down emission sources and locate other pollution trouble spots, ooze over to Enviromapper from the U.S. Environmental Protection Agency. The site offers 11 modules for charting environmental variables. The Envirofacts module, for instance, can pinpoint everything from contaminated streams to air polluters. Zoom in and click on any source to find out how much of each chemical it releases. With another feature, users can flush out results of soil, water, and sediment tests conducted at locations such as schools and petrochemical plants after last year's Gulf Coast hurricanes. >> www.epa.gov/enviro/html/em/index.html

Success is based on knowledge, not chance



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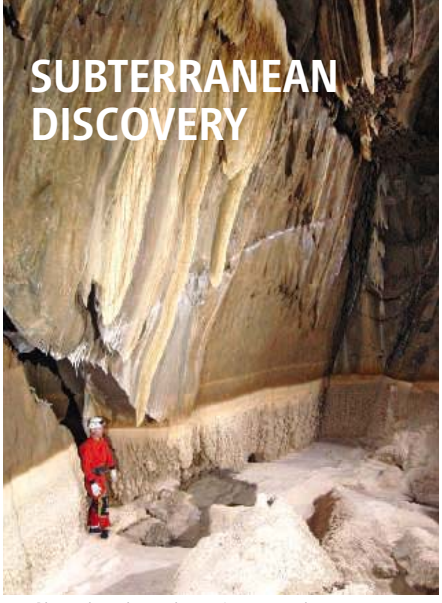

Glittering interior of Ursa Minor.

A newly discovered, millions-of-years-old cave in California's Sequoia National Park could house new species as well as clues to the age of the Sierra Nevada mountains.

The cave was dubbed Ursa Minor after a bearlike skeleton found inside as well as the starlike sparkle of its crystal-encrusted walls and floors. Researchers have yet to explore the entire cave, which was found in August by explorer Scott McBride of the Cave Research Foundation. It is at least 300 meters long with several large rooms and a lake roughly 30 meters across. The cave is adorned by long, flowing formations known as cave curtains, as well as stalagmites and thin, hollow stalactites known as soda straws up to 2 meters long hanging from the ceiling.

At least 27 new species have been discovered in the 240 caves in the area, including pseudoscorpions, millipedes, and spiders. "We almost expect to find new species" in this one, says the park's cave specialist, Joel Despain. Dating of old river levels recorded by Ursa Minor could also help settle a heated debate about the Sierra Nevada's age, says Despain. The mountains have been estimated to be anywhere from 10 million to 100 million years old.

Parasite Favors Boys?

A common parasite may be influencing the sex composition of the world's human population.

Toxoplasma gondii, which people often pick up from cats, infects between 20% and 80% of societies worldwide. Parasitologist Jaroslav Flegr and his colleagues at Charles University in Prague studied the medical records of 1803 infants born in three maternity clinics in Prague that routinely test for antibodies to toxoplasma, which can cause miscarriages and birth defects. The usual sex ratio at birth is 104 boys for every 100 girls. But the 454 pregnant women who tested positive gave birth to 290 boys and only 187 girls. The women with the highest antibody levels had more than twice as many boys as girls, the team reports this month in *Naturwissenschaften*.

Flegr says the parasitic infection may suppress the maternal immune system, which sometimes reacts against male embryos and causes more boys to be miscarried. Larger samples are needed, but the data are intriguing, says parasitologist Joanne Webster of Imperial College London. What isn't clear, she adds, is the evolutionary advantage that the parasite might get from skewing the sex ratio.

No Nine Lives for Cat Cloners >>

Genetic Savings & Clone, which fancied itself a pioneer in the brave new world of pet cloning, is folding after 6 years in business during which it cloned just six cats and sold two to pet owners. Customers of the Sausalito, California–based company who want to bank their pet's DNA have been directed to ViaGen, an Austin, Texas, company that clones livestock. It seems the price was just too stiff—even though last year the company dropped its fees from $50,000 to $32,000—and the procedure hasn't gotten any more efficient since the first cat was cloned in 2002 (*Science*, 22 February 2002, p. 1443), says Charles Long of Texas A&M University in College Station, an adviser to the company.

But pet cloning's day will come. A spokesperson at Global Genetics and Biologicals in Bryan, Texas, a storage company, says it's got about 150 dog and cat samples on ice, waiting until the price is right.

OLDEST WALL ART YET FOUND

French archaeologists working in Syria this summer found what they contend are the earliest known wall paintings, based on radiocarbon dates of about 11,000 B.C.E. from a mud-brick building at the early farming site of Dja'de el-Mughara. The structure, which has about 4 square meters of geometric paintings on its interior walls, was roughly shaped like a bull's head and apparently was used for ritual activities, says excavation director Eric Coqueugniot of the French research agency CNRS in Lyons.

The dating makes the designs at least 1500 years older than wall paintings at Çatalhöyük, the famous 9500-year-old Turkish village (*Science*, 20 November 1998, p. 1442). Cave art dates back 36,000 years, but it was not until the so-called Neolithic Revolution that people began marking up humanmade surfaces.

Archaeologist Tristan Carter of Stanford University in Palo Alto, California, says the new find bears on the question of whether the transition from hunting and gathering to farming was more a result of a "symbolic revolution" or a response to external circumstances. Recent finds, including the discovery of sculptures at other very early Near Eastern sites, show that "the symbolic worlds of these Neolithic peoples have to be addressed as a means of understanding these societies," he says.

Climate fix?
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EPIDEMIOLOGY

Iraqi Death Estimates Called Too High; Methods Faulted

A new estimate of the number of Iraqis who have died as a consequence of the U.S.–led invasion in March 2003 has ignited a firestorm of its own. At 400,000 to 800,000 deaths, the new number is at least 10 times higher than estimates cited by the Iraqi government and U.S.–led coalition. U.S. President George W. Bush immediately dismissed the study, characterizing its methodology as "pretty well discredited." Other Administration officials charged that the study, released with significant publicity 4 weeks before U.S. midterm elections, was politically motivated. Researchers who spoke with *Science* disagree that the authors' motives are suspect but raise several questions about the methodology of the study, which was published 11 October in *The Lancet*.

Counting the dead. Researchers attribute most of the estimated 400,000 to 800,000 Iraqi deaths to violent causes, including gunshots, air strikes, and car bombings, such as this one in Baghdad.

CREDIT: ALI JASIM (IRAQ)/REUTERS

Experts on both sides of the debate concede that it is notoriously difficult to get an accurate count of casualties in Iraq. The Iraqi Ministry of Health has estimated up to 40,000 violent deaths so far, based on death certificates reported by hospitals and morgues. That figure falls within the range published by Iraqi Body Count, an independent London-based group opposed to the war that compiles casualty numbers from media reports. There is little doubt that the real number of deaths is higher than this, because only a fraction of deaths are officially recorded or reported by journalists. But just how small is that fraction?

The *Lancet* study, designed by researchers at Johns Hopkins University in Baltimore, Maryland, is based on a survey conducted between May and July by a team of 10 Iraqi health workers. (The Johns Hopkins researchers met with the Iraqi team twice across the border in Jordan to advise on the survey techniques.) The team visited 47 neighborhoods in 18 different regions across the country, going door-to-door and asking families about recent deaths. They collected data from a total of 1849 households containing 12,801 residents. For the 14 months before the invasion, the Iraqi families reported 82 deaths, an annual death rate of 5.5 per 1000 people. Within the same households, 547 people died between the start of the invasion and July of this year—an annual increase of 7.8 deaths per 1000. By applying this rate to the entire population of 27 million, the researchers conclude that 655,000 more Iraqis have died than would have if the invasion had never happened. About 8% of these extra deaths are attributed to deteriorating public health, but an estimated 601,000 are violent—56% from gunshots and about 13% each from air strikes, car bombs, and other explosions. The researchers calculate a 95% probability that the true number of violent deaths lies between 426,369 and 793,663.

Many academics spoke up in defense of the study. "I too find the survey's estimates shockingly high, … [but] the choice of method is anything but controversial," wrote Francesco Checchi, an epidemiologist at the London School of Hygiene and Tropical Medicine on 12 October on a humanitarian Web site. The statistical technique used, called cluster surveying, divides the population into different regions, neighborhoods, and households, in contrast to a random sampling of people on the streets.

The method may be sound, but several critics question the way it was carried out in this study. Madelyn Hicks, a psychiatrist and public health researcher at King's College London in the U.K., says she "simply cannot believe" the paper's claim that 40 consecutive houses were surveyed in a single day. "There is simply not enough time in the day," she says, "so I have to conclude that something else is going on for at least some of these interviews." Households may have been "prepared by someone, made ready for rapid reporting," she says, which "raises the issue of bias being introduced."

Lead author Gilbert Burnham, an epidemiologist at Johns Hopkins, counters that "40 adjacent households is entirely achievable in a day's work if well organized." Les Roberts, also at Hopkins, adds that 80% of the 547 deaths were corroborated with death certificates. The fact that hundreds of thousands of death certificates seem to have gone unregistered by the Ministry of Health is no surprise, says Roberts, because "those have always been grossly underreported."

Neil Johnson and Sean Gourley, physicists at Oxford University in the U.K. who have been analyzing Iraqi casualty data for a separate study, also question whether the sample is representative. The paper indicates that the survey team avoided small back alleys for safety reasons. But this could bias the data because deaths from car bombs, street-market explosions, and shootings from vehicles should be more likely on larger streets, says Johnson. Burnham counters that such streets were included and that the methods section of the published paper is oversimplified. He also told *Science* that he does not know exactly how the Iraqi team conducted its survey; the details about ▶

neighborhoods surveyed were destroyed "in case they fell into the wrong hands and could increase the risks to residents." These explanations have infuriated the study's critics. Michael Spagat, an economist at Royal Holloway, University of London, who specializes in civil conflicts, says the scientific community should call for an in-depth investigation into the researchers' procedures. "It is almost a crime to let it go unchallenged," adds Johnson.

Co-author Roberts is no stranger to such controversy. He led a smaller study of Iraqi casualties, published in *The Lancet* in 2004, that estimated 100,000 deaths. That work was criticized for relying on too few samples. This time, he says, "we took enough samples, and if anyone wants to verify our results, it's easy." The study suggests that close to four times the number of deaths occurred in the first half of 2006 than in the first half of 2002, he says, "and anyone could simply pick four to six spots in Iraq and go to the local graveyards. The increase … should be obvious."

For now, Spagat says he is sticking with casualty numbers published by the United Nations Development Programme (UNDP). A UNDP survey of 21,668 Iraqi households put the number of postinvasion violent deaths between 18,000 and 29,000 up to mid-2004. "When a survey suggests so much higher numbers than all other sources of information," he says, "the purveyors of this outlier must make a good-faith effort to explain why all the other information is so badly wrong." **–JOHN BOHANNON**

ECOLOGY

Report Warns of Looming Pollination Crisis in North America

California almonds are a huge food crop in the United States, and land devoted to almond trees is expected to increase another 50% by 2012. But that growth depends in large part on availability of the almonds' pollinator, the honeybee.

And honeybees are in trouble, according to a report on North American pollinators* unveiled this week by the National Research Council (NRC) of the National Academies. Although there is "no strong evidence for a current pollination crisis," there may be one looming, reports an NRC committee led by entomologist May Berenbaum of the University of Illinois, Urbana-Champaign.

The committee calls for better long-term monitoring of all pollinators, noting that few records exist for species other than honeybees. A study earlier this year documented decreasing pollinator diversity in Europe, and there are similar fears about what's happening in North America (*Science*, 21 July, p. 286). Last year, for the first time since 1922, California almond growers imported bees from Australia to service their trees because U.S. bee colonies are being decimated by a mite, *Varroa destructor*, which sucks the life out of larvae. According to the report, the mite, which first showed up in 1987, is even overshadowing the Africanized honeybee, which—adaptable, angry, pushy, and proliferative—has been steadily encroaching in the southern United States and muscling aside the gentler European honeybee population.

Roughly one-third of the North American diet comes from food—fruits, vegetables, seeds, and nuts—that rely on animal pollinators, which include beetles, butterflies, flies, bats, hummingbirds, and bumblebees. But the king of pollinators is *Apis mellifera*, the European honeybee. Much preferred over its African cousin, it's a "generalist" that pollinates a huge variety of crops. It is also highly social and thus easy to muster.

Stamps of approval. Next spring, the U.S. Post Office will issue these and other stamps depicting pollinators.

CREDIT: UNITED STATES POSTAL SERVICE

The NRC report notes that just as modern agriculture relies too much on monocultures, there is too much reliance on honeybees, which beekeepers truck around from one crop to another, like migrant workers. Almonds are particularly vulnerable, says Kevin Hackett of the Agricultural Research Service, because their trees flower early in the year when honeybee colonies are weakened from winter mite infestations. He says mites have caused the price of bee rental for almond growers to go from about $30 to as much as $150 per hive.

NRC calls for more research on the mite problem, noting that *Varroa* have become resistant to antibiotics and pesticides. It's been difficult to breed mite resistance into the bees, in part because of the queens' loose mating habits. Hence the need, says the committee, to develop "non-*Apis*" pollinators such as the alfalfa leaf-cutter bee, which doesn't have a mite problem.

The committee also advises that the U.S. government establish discovery surveys for wild pollinators of U.S. crops and of rare or endangered plants. The NRC report adds that beyond increased research and data-gathering, simple steps, such as growing wildflowers in golf-course roughs, can help keep a diverse array of pollinators in business.

Adding to the buzz surrounding the report, the 3-year-old North American Pollination Protection Campaign (www.pollinator.org) sponsored a symposium this week at USDA to discuss better management of pollinator resources worldwide.

–CONSTANCE HOLDEN

* *Status of Pollinators in North America*, www.nap.edu/catalog/11761.html

EUROPEAN FACILITIES

Panel Draws Up Shopping List

European researchers have compiled a wish list of 35 large-scale projects that they would love to see built over the next 2 decades. The projects, which must be internationally important and open to all European researchers, include a database on the impacts of population aging, a polar research ship, and an underwater neutrino observatory. John Wood, head of the U.K.'s Central Laboratory of the Research Councils and chair of the panel that drew up the road map, says the list released this week will help potential funders "to see what's out there, what's likely to come up, and when." The hope is that it will become an informal priority list of international European projects.

The road map was put together by the European Strategy Forum on Research Infrastructures (ESFRI), a meeting place for officials and senior scientists from the European Union and individual nations to work out collaborations on big projects. Projects for the road map "had to demonstrate added value at a European level," says Ruth Barrington, head of Ireland's Health Research Board, who chaired the road map's biological and medical science working group, one of three such subgroups. Projects in space science and high-energy particle physics were excluded from the road map because they fall under the purview of the European Space Agency and CERN, the European particle physics lab near Geneva, Switzerland.

The projects range in cost from the €9 million ($11 million) European Social Survey to the €1.2 billion Facility for Antiproton and Ion Research. Although the road map gives no guarantee of funding, it "will give the message [to researchers] that they must get organized at a European level if they're going to get new infrastructures," says Carlo Rizzuto, head of the Sincrotrone Trieste laboratory in Italy, who led the road-map working group on physical sciences and engineering.

Although big facilities in the physical sciences are commonplace, ESFRI tried hard to work life sciences, social sciences, and humanities into the mix. "We took a wide-ranging decision that we must include all disciplines," says Barrington. Bjørn Henrichsen of Norwegian Social Science Data Services, who headed the social science and humanities working group, says this is the first time social sciences were treated the same as natural sciences in such a process. But despite ESFRI's efforts to be inclusive, several areas of research are not represented in the list, such as geology, engineering, energy research, psychology, and economics. "I hope communities will become excited by the vision of the road map" and bid to be included in future versions, says Wood.

Rizzuto hopes that the road map will help promote the idea of open-access facilities. "This mode of infrastructure has existed since the Middle Ages, but it still needs to be explained to politicians," he says. Barrington thinks the "convergence of thinking" that went into the road map and the support from senior scientists and government officials has been "absolutely remarkable."

ESFRI members will present the road map next spring at a Paris meeting of the Organisation for Economic Co-operation and Development on research infrastructure. Will that meeting result in a world road map? "Wouldn't that be lovely?" says Wood.

–DANIEL CLERY

New life. The ESFRI road map includes upgrades to the European Synchrotron Radiation Facility (*top*) and the Institut Laue-Langevin neutron source.

CREDITS (TOP TO BOTTOM): ASSA; ILL/ARTECHNIQUE

New Controls on North Korea

Japan is likely to go beyond United Nations sanctions in an effort to clamp down on trade with North Korea in the wake of its underground nuclear test.

Four years ago, Japan introduced a catchall system to prevent exports to North Korea of technologies useful for developing weapons of mass destruction. The small yield of last week's explosion has prompted speculation that it was a test of a bomb miniaturized for placement on a missile. Japanese officials had already tightened export controls after North Korea's missile tests last July, adding large cranes and trucks to the list of sensitive items that could be used for missile launchers. "We placed a very close watch on North Korea–related entities in Japan," says Naoyuki Hasegawa, director of the security export control policy division at the Ministry of Economy, Trade, and Industry. Since July, Hasegawa says, investigators have detected "a few cases of possible or plausible diversion" of such items via Singapore. He says the ministry is now reviewing ways to further tighten its export regime.

–RICHARD STONE

They're Resolute on Institute

Despite a resounding lack of support from almost every group it is supposed to reach, the planned European Institute of Technology (EIT) is still moving forward. This week, European Union leaders issued formal plans for spending €2.4 billion ($3 billion) over 5 years on the university, which is supposed to help close what politicians see as Europe's "innovation gap." Initially floated in 2005 by European Commission president José Manuel Barroso, the EIT has been roundly criticized by scientists and university leaders as ill-conceived and a potential waste of money and effort (*Science*, 3 March, p. 1227).

Now comes news that industry isn't impressed either. Last week, Barroso's office confirmed that €800 million in hoped-for financial support from companies had not materialized. Yet this week, the commission presented its proposed regulations for governing the institute, via a board that would choose European researchers to form networks called "knowledge and innovation communities." The proposal still needs approval from the European Parliament and the council of ministers, but critics have largely given up hope of blocking the school's creation, says Geoffrey Boulton of the University of Edinburgh in the U.K. He hopes now "to try to steer it" in a productive direction.

–GRETCHEN VOGEL

Top plans. The Technical University Munich is one of three winners in Germany's elite university competition.

HIGHER EDUCATION

A German Ivy League Takes Shape

BERLIN—In world rankings of universities, Germany's institutions come out solidly in the middle of the class. The 2006 list drawn up by the *Times Higher Education Supplement*, for example, puts the University of Heidelberg at number 58, and that's the best of any German university. Last year, the German government launched an "excellence initiative" that would boost at least a few universities to world-class status—a German Ivy League. Schools around the country have applied for the €1.9 billion ($2.38 billion) budgeted to the initiative, and the first results of this competition, announced last week, give Munich major bragging rights: Two of the three universities singled out as potential topflight schools are the Technical University Munich (TUM) and the Ludwig Maximillian University (LMU), also in Munich. The third is the Technical University (TU) Karlsruhe, in southwest Germany. In a surprise, Heidelberg didn't make the cut—at least this time.

The idea of a few top universities that attract the best and the brightest is hardly new in most Western countries, but in Germany it challenges the status quo. For decades, official policy has been that the state-financed, tuition-free universities should all be roughly comparable in quality and prestige. But after years of flat or even shrinking budgets, universities are largely seen as burdened with aging infrastructure, growing student loads, and a hierarchical faculty system that leaves little room for up-and-coming researchers. Instead, many of Germany's best scientists are concentrated at the nonacademic Max Planck institutes and at research centers of the government-funded Helmholtz or Leibniz associations.

The new initiative introduces a taste of the interuniversity competition that keeps U.S. schools on their toes, says Peter Strohschneider, head of the German Science Council: "We are erasing the popular fiction that all German universities are equal."

Still, when former science and education minister Edelgard Bulmahn announced her idea for a German "elite university" in early 2004 (*Science*, 9 January 2004, p. 155), some politicians and academic administrators worried that lavishing money on a few schools would leave the rest of the chronically underfinanced system to decay. Others noted that investing the planned €1.9 billion over 5 years could hardly create a Harvard or Stanford—which have yearly budgets of $3 billion each. And some feared that politicians would water down the program by spreading the funding throughout the country.

Indeed, in a compromise worked out after more than a year of wrangling between Germany's federal and state officials, the program was widened to include three award categories: €1 million a year for new graduate schools, €6.5 million for so-called excellence clusters designed to spark cooperation between universities and neighboring research institutes, and a top award of about €13 million annually for schools that develop promising strategies to "advance top-level research." In the results announced on 13 October, 22 universities were awarded the extra funding for new graduate school programs and excellence clusters. TU Karlsruhe, TUM, and LMU were among those winners, but they were also tabbed for the most-coveted university-wide award.

The selections quieted some critics who predicted that the money would flow based on political calculations instead of academic criteria. Indeed, at last week's meeting between 26 scientific reviewers and the 17 state and federal science ministers, several politicians complained that the scientists—who had a majority of the votes—gave them no voice in the final decision. After a few heated comments, however, the politicians accepted the scientists' recommendations without dissent. Although there were scattered winners in Berlin, Hanover, and Kiel, most of the funding will flow to schools in the southern half of the country. The University of Dresden was the only school in the former East Germany with any winning projects. Federal science minister Annette Schavan acknowledged the tension behind the awards, but she called the unanimous vote "a sign of confidence from the politicians" in the scientists' judgement.

German Chancellor Angela Merkel, who trained as a physicist, also defended the awards, noting that the long-term research investments made by southern regions paid off. "If the south is better, then that's the way it is," she told journalists.

TU Karlsruhe, with 18,000 students, played up its long-standing cooperation with the Forschungszentrum Karlsruhe, an institute governed by the Helmholtz Association, with 1400 scientists in materials science, environmental sciences, energy, and health. The two bodies will together create the Karlsruhe Institute of Technology, modeled on the Massachusetts Institute of Technology, which is much admired across Europe for attracting top talent and spinning off patents and products. Rector Horst Hippler notes that the extra €21 million a year will be helpful, but much more important, he says, will be the image boost the school hopes to receive.

TUM called its concept "the entrepreneurial university" and says it plans to increase cooperation with for-profit partners. It also plans to further develop its new Institute for Advanced Studies, modeled on the one in Princeton, New Jersey, which will free some of its top professors from part of their teaching loads.

LMU, with 47,000 students, says it will use its extra funds for a multidisciplinary Center for Advanced Studies, focused on "problem-oriented" research. It also plans to boost its private fundraising—still a rarity among German universities.

Heidelberg and others disappointed by this week's announcement will have another chance next year, when an additional €1 billion will be distributed in a second round of funding. **–GRETCHEN VOGEL**

CREDIT: THORSTEN NAESER

ATMOSPHERIC SCIENCE

Pollute the Planet for Climate's Sake?

The source of the proposal was almost as remarkable as the idea itself. In the August issue of *Climatic Change*, Paul Crutzen, who won the Nobel Prize for helping work out the chemistry of ozone destruction in the stratosphere, resurrected an oft-disparaged suggestion: Create a global haze by spewing megatons of sulfurous debris into the stratosphere to shade the planet and rein in greenhouse warming. "A few years ago, I would have said, 'I'm not touching that,' " says the Max Planck Institute for Chemistry researcher. Now, however, he finds the "grossly disappointing international political response" to global warming's threat so disturbing that the notion of deliberately contaminating the stratosphere looks less and less crazy.

Bad idea, respond some climate scientists. It would be applying a Band-Aid to the symptom while continuing to stoke the problem with ever-increasing greenhouse gas emissions. Best not even to talk about it. Worth looking at, say others. Given the surprises that may be lurking in the greenhouse, desperate countermeasures could come in handy. Thanks to Crutzen's stature, this scientific and ethical debate is blossoming as the climate community begins to take a hard look at geoengineering climate.

Supporters of at least studying the idea seem to have some momentum for now. "Crutzen's paper created some sort of phase change, making geoengineering a respectable topic of conversation," says climate modeler Kenneth Caldeira of the Carnegie Institution Department of Global Ecology at Stanford University.

Geoengineering as a fix for global warming has been a topic of usually sotto voce conversation since the 1970s, when the Soviet climatologist Mikhail Budyko suggested Earth could be cooled by adding tiny sunlight-reflecting particles to the stratosphere. Nature soon served up a couple of striking examples of how it might be done when the volcano El Chichón erupted in 1982 and Mount Pinatubo erupted in 1991. The long-lived stratospheric debris of Pinatubo—water droplets laced with sulfuric acid derived from the volcano's sulfur—reflected enough sunlight back into space to cool Earth on average 0.5°C for a year or two following the eruption. That's about the size of the warming of the past century.

A volcanic chill. Humans might loft sulfur into the stratosphere to counteract global warming; Mount Pinatubo did in 1991.

CREDIT: BULLIT MARQUEZ/AP PHOTO

Pulling off a "human volcano" to counteract global warming would take some wherewithal. Pinatubo put up 10 million tons of sulfur, most of which fell out of the stratosphere within 2 or 3 years. So humans looking to cool the greenhouse by stratospheric shading would have to send millions of tons of sulfur tens of kilometers into the air every year, perhaps century after century, in order to renew the continually depleted shield of haze. The resulting acid rain would be minor compared to current levels, say proponents. People have discussed delivery methods from balloons, big guns, and giant planes. To ease the burden of lifting megaton masses, the late Edward Teller—father of the hydrogen bomb and "Star Wars" missile defense advocate—proposed substituting more efficient reflectors for sulfur, something metallic and perhaps engineered like tiny retroreflectors. ▶

Pass the Hat for Alien-Hunting

With NASA scaling back funding for astrobiology, scientists are turning to California's Silicon Valley to keep hope alive. The SETI Institute in Mountain View, whose more than two dozen researchers rely on NASA astrobiology grants, plans to create a new privately funded center devoted to the study of life in space. Organizers are looking for up to $6 million over the next 3 years, says SETI's Scott Hubbard, with funds aimed at retaining staff and expanding research at the newly named Carl Sagan Center. The community took a similar approach after lawmakers refused to fund extraterrestrial intelligence research a decade ago.

–ANDREW LAWLER

Crawford Pleads Guilty

A former head of the U.S. Food and Drug Administration (FDA) pleaded guilty this week to owning shares of stock in companies the agency regulates and filing false financial disclosure forms saying he had sold them. Lester Crawford, a pharmacologist and veterinary medicine specialist who resigned his post suddenly last fall after just 2 months, was charged with two misdemeanors for withholding financial information. The Justice Department complaint states that Crawford, who spent 8 years at FDA in three separate stints, or his wife owned shares in soft-drink maker Pepsico while he chaired an FDA obesity working group.

"There's little that we can do if people do not provide honest disclosures of financial interest," says Jeremy Sugarman, a bioethicist at Johns Hopkins University in Baltimore, Maryland. Sentencing is set for January.

–JENNIFER COUZIN

Biosafety Lab Delayed

A U.S. nuclear-weapons lab must conduct another environmental review before opening a biosafety level 3 lab on its grounds, a federal appeals court ruled this week. The move is a win for activists led by the Livermore, California, based Tri-Valley Cares, which had sued the Department of Energy's Lawrence Livermore National Laboratory over the proposed facility in 2003. Such a review, which must consider the possibility of a terrorist attack on the lab, could take a year. Livermore says it is mulling its options; activists hope the decision will bolster efforts to thwart other planned biosafety labs at government facilities. Livermore had planned to open the lab as soon as next month (*Science*, 13 October, p. 235).

–ELI KINTISCH

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Daunting practical aspects aside, the latest—although preliminary—climate modeling hints that shading the globe to counteract greenhouse warming could actually work. In this issue of *Science* (p. 452), climate researcher Tom Wigley of the National Center for Atmospheric Research in Boulder, Colorado, reports that in a simple, so-called energy-balance model, firing off a Pinatubo eruption every 2 years or so would be enough to counteract the projected warming indefinitely. And so far in sophisticated general circulation models (GCMs), "all the simulations have suggested it would basically work," says Caldeira, who has run many such simulations. Crutzen, who has been cooperating on other GCM simulations, agrees. "It's very tantalizing," he says. "It just looks too good."

That's what worries many climate researchers. "I refuse to go down that road," says biogeochemist Meinrat Andreae of the Max Planck Institute for Chemistry in Mainz, Germany. "You're papering over the problem so people can keep inflicting damage on the climate system without having to give up fossil fuels." That option could be so attractive that "the biggest risk of geoengineering is it eliminates pressure to decrease greenhouse gas emissions," says Caldeira.

Other critics note that if a shading effort faltered, decades or centuries of greenhouse warming would envelop the world in a couple of years. Nonclimate effects of carbon dioxide, such as acidification of the oceans, would continue apace despite the shading. And then there's the complexity of the climate system. Recent model simulations aside, "we don't know exactly what is going to happen" once stratospheric shading begins, says climate modeler Lennart Bengtsson of the Max Planck Institute for Meteorology in Hamburg. All things considered, many climate scientists would just as soon see geoengineering of the climate problem returned to obscurity.

Ignoring the idea has its appeal, admits climate modeler Michael MacCracken of the Climate Institute in Washington, D.C., but "the question comes up so many times, you have to be addressing it." And studying the possibility wouldn't mean it would have to be done, says geoscientist Michael Oppenheimer of Princeton University. Quite the opposite. The idea of sucking the greenhouse's carbon dioxide into the deep sea by fertilizing ocean phytoplankton with iron only went away, he notes, after small-scale experiments showed it wouldn't work as proponents hoped (*Science*, 11 August 1995, p. 759).

A human volcano has obvious drawbacks, concedes Ralph Cicerone, an atmospheric scientist and president of the U.S. National Academy of Sciences, but they may appear to dwindle in the future. If warming took off far faster than expected, for example, and serious efforts to cut back greenhouse gas emissions were failing, a stopgap approach would become more attractive, he says. A scientific understanding of the shading option should be in hand in case that happens, he argues; scientists could study geoengineering while agreeing not to carry it out on a large scale. The U.S. Department of Energy seems to agree. Officials there, emboldened by Crutzen's paper, are taking a renewed interest in stratospheric shading, arranging workshops and a meeting next year while considering releasing a report on the subject.

–RICHARD A. KERR

PHYSICS

Voilà! Cloak of Invisibility Unveiled

Just 5 months after predicting it should be possible, a team of physicists has produced a cloaking device that renders an object invisible—at least when viewed in microwaves of a particular wavelength.

The cloak is hardly perfect: Instead of an all-concealing sphere, it's a ring that works only for microwaves zipping along in a plane. The microwaves must also be polarized perpendicular to the plane. And even then, the cloak reflects some of the waves and casts a slight shadow. Nevertheless, "it's a very good achievement," says Ulf Leonhardt, a theorist at the University of St. Andrews in the United Kingdom. "It's surprising that it's as simple as it is and that it works so well."

The cloak embodies the theory laid out by theorist John Pendry of Imperial College London and experimenters David Schurig and David Smith, who work in the electrical and computer engineering department at Duke University in Durham, North Carolina. In May, the team showed that, in principle, it's possible to ferry electromagnetic waves such as light around an object by surrounding it with a "metamaterial": an assemblage of tiny rods and C-shaped rings (*Science*, 26 May, p. 1120). The waves would then pass as if the object weren't there, rendering it invisible.

The electromagnetic waves cause the electrons in the rings and rods to slosh, and the sloshing, in turn, affects the speed at which the waves travel through the material. If the speed varies in the right way within the cloak, the waves will curve around the object. The theory predicts only how the speed of the waves must vary; it leaves it to experimenters to design the material.

Where'd it go? This cloaking device is practically invisible—if you see the world in microwaves with a wavelength of 3.5 centimeters.

CREDIT: DAVID SCHURIG

When Schurig, Smith, and colleagues worked out the details, they found that their two-dimensional device required only C-shaped copper rings nestled side by side. The team also simplified the parameters specified by the theory. The changes made the metamaterial easier to build but also left the cloak slightly reflective, as the team reports online this week in *Science* (www.sciencemag.org/cgi/content/abstract/1133628). "The goal of this paper was to demonstrate that we more or less have the mechanism and that we can design the materials to the parameters," Schurig says.

Even the simplified cloak is a significant advance, says Costas Soukoulis, a theorist at Iowa State University in Ames and the U.S. Department of Energy's Ames Laboratory. "This is very, very important that experiments have produced what theorists had predicted," Soukoulis says. Microwave cloaks might be useful for eluding radar, he says.

It may take years for researchers to make a cloak for visible light. Still, most believe such a thing should be possible now that a cloak for microwaves has been built. After all, not seeing is believing. **–ADRIAN CHO**

ECOLOGY

A Rescue Effort for Tsunami-Ravaged Mangrove Forests

KOH PHRA THONG, THAILAND—Fishers in longboats putter down a waterway in a mangrove forest on Phra Thong Island, a lesser adjutant soaring gracefully overhead. The tsunami of December 2004 dealt a vicious blow to Phra Thong, in the Andaman Sea, wiping out one of three villages and wrecking tropical forests and savanna. Now, the island's rebounding mangroves exemplify how ravaged coastal ecosystems can be restored, and how rare species such as the lesser adjutant—a black-and-white member of the stork family with a 2-meter wingspan—might mount a comeback.

At a 31 October gathering of tsunami donors at the United Nations, the World Conservation Union (IUCN) and the U.N. Development Programme are planning to unveil a 6-year, $62 million initiative called Mangroves for the Future (MFF). Its goal is to replicate success stories like Phra Thong by replanting mangroves, rebuilding sand dunes, restoring sea-grass beds, and otherwise rehabilitating ecosystems in 12 tsunami-hit nations. "It's a tiny amount of money" compared to the $8.25 billion committed so far to post-tsunami reconstruction, says Lucy Emerton, head of IUCN's Ecosystems and Livelihoods Group. But for the 640 million people living within 100 kilometers of the coast in countries involved in the initiative, she says, "the payoff is potentially huge."

Mangrove forests shelter wildlife, serve as a source of food, herbs, and firewood, and act as a buffer against wind and waves. Although Asia boasts nearly 40% of the world's mangrove coverage, it was losing the fragile wetlands at an alarming rate even before the tsunami: Between 1980 and 2000, India, Indonesia, Sri Lanka, and Thailand lost nearly a third of their total mangrove area, IUCN notes. Clearance for settlements and conversion to shrimp farms are major reasons for the declines. "So much of what we're seeing is the cumulative effect of decades of neglect and bad policies that the tsunami brought into sharp focus," says Emerton. On Phra Thong, mangrove trees were clear-cut to make charcoal until Thailand banned the widespread practice in 1991, says IUCN's Somsak Soonthornnawaphat. As a result, over the past 2 decades, mangroves in Phra Thong, off the Kra Isthmus connecting Thailand and Malaysia, have been growing back.

Spiritual joy. A Moklen boatsman prepares to head out to sea via a protected mangrove forest on Phra Thong Island. A new initiative intends to replicate the successful restoration of mangroves here in other tsunami-hit areas.

Tsunami damage was magnified in areas with degraded coastal ecosystems. On Sri Lanka's south coast, for instance, one hotel that had leveled a sand dune "suffered enormous damage from the tsunami," Emerton says, while another nearby that had retained its dune suffered little. The simple lesson, she argues, is that intact ecosystems help protect coastal infrastructure.

Mangroves are resilient to wave action, yet the tsunami overpowered many forests, including one in southern Phra Thong. (An eastern forest emerged mostly unscathed.) IUCN is working with Thai authorities to replant mangroves there and set up nurseries under a recovery plan crafted with the Swiss Agency for Development and Cooperation.

As part of this strategy, the Moklen people, or "sea gypsies" who island-hopped before settling on Phra Thong in the early 1900s, have demarcated a "community mangrove forest" in which fishing, cutting trees, and dumping oil are prohibited. IUCN and other agencies have helped the Moklen augment their food supply through organic farming of plants such as basil and galangal that thrive in sandy soil. "Before the tsunami, we only knew about the sea," says Galaya Petchsai, a Moklen in Thung Dap village. She and other Moklen trap crabs and squid to trade for rice and other goods; the introduction of gardens increases their self-sufficiency, says Somsak.

In addition to replicating the strides made at Phra Thong, MFF intends to fund an updated assessment of mangrove distribution in the countries hit by the tsunami. "It's a huge gap," says Emerton. Another goal is to strengthen the science of ecosystem restoration. After the tsunami, "there were a lot of well-intentioned but misguided attempts at mangrove restoration" throughout Southeast Asia, Emerton says. "A lot of money went into trying to plant mangroves where they can no longer grow or could never grow."

An MFF work plan will be presented to donors at the 31 October meeting, hosted by former U.S. President Bill Clinton, U.N. special envoy for tsunami recovery. Projects will begin in January. "We don't want to lose the momentum," Emerton says. "There is a limited window of opportunity to persuade countries and donors that they should be investing in ecosystems."

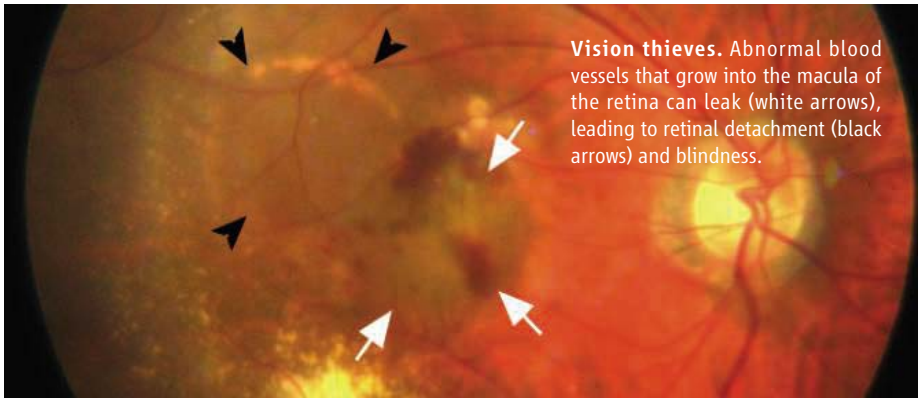
For the Moklen, MFF should please the gods. Many believe the tsunami was divine retribution for how people harmed the land. "Now that there is no more cutting or destroying," says Petchsai, "maybe the spirits are happy." **–RICHARD STONE**

CREDIT: MUTSUMI STONE

GENETICS

Gene Offers Insight Into Macular Degeneration

Within the past year, researchers have begun identifying the gene changes underlying age-related macular degeneration (AMD), the common eye disease that can eventually rob people of their vision. Some of the responsible genes are involved in inflammatory responses, which can cause tissue damage if not properly controlled (*Science*, 24 March, p. 1704). Two reports, published online this week by *Science* (www.sciencemag.org/cgi/content/abstract/1133807 and www.sciencemag.org/cgi/content/ abstract/1133811), now point to the possible involvement of another gene—and another pathogenic mechanism—in AMD development.



Vision thieves. Abnormal blood vessels that grow into the macula of the retina can leak (white arrows), leading to retinal detachment (black arrows) and blindness.

Josephine Hoh of Yale University School of Medicine and her colleagues came upon the new candidate, known as *HTRA1*, by studying a group of Chinese patients who have AMD's more severe "wet" form, which is caused by the abnormal growth and breakage of blood vessels in the macula, the central part of the retina. At least in Caucasian populations, wet AMD often occurs in patients who first develop drusen, abnormal macular deposits of proteins and other materials. But the 96 Chinese patients Hoh examined had few or no drusen. They "go directly into the wet form," she says.

The Yale team ultimately found a single-nucleotide polymorphism (SNP)—a change of one DNA base—on chromosome 10 that distinguished the patients from people without AMD. Similarly, Kang Zhang and his colleagues at the University of Utah School of Medicine in Salt Lake City have found an association between the same SNP and AMD, but in a Caucasian population whose wet AMD is compounded by a large amount of drusen.

This is not the first time this chromosome region, known as 10q26, has turned up in screens for AMD genes. For example, last year Michael Gorin's team at the University of Pittsburgh School of Medicine in Pennsylvania reported that 10q26 contains three potential AMD genes, *PLEKHA1*, *LOC387715*, and *HTRA1* (also known as *PRSS11*). At the time, Gorin says, his analysis indicated that *LOC387715*, a putative gene of unknown function, showed the strongest linkage to AMD, a conclusion that has received support from other researchers.

The work of Hoh's and Zhang's teams suggests that *HTRA1* is the better candidate. Both teams found the suspicious SNP within *HTRA1*'s regulatory sequences, and preliminary biochemical studies by the Yale group indicate that the SNP increases production of *HTRA1*'s protein. Consistent with that finding, Zhang and his colleagues have detected elevated expression of the gene in retinal tissue from four deceased AMD patients who carried the high-risk *HTRA1* variant.

What's more, the gene appears to be involved in the development of the light-detecting cells of the retina. Earlier this year, Anand Swaroop and his colleagues at the University of Michigan, Ann Arbor, showed that its expression increases just as the cells begin to take on their final form. "I think it's going to be an important gene," says Swaroop, who has his own as-yet-unpublished evidence linking it to AMD. "*HTRA1* is a great [AMD] candidate," Gorin agrees.

The gene encodes a protein-splitting enzyme, hinting that it might contribute to retinal damage. The enzyme also interacts with other proteins, such as TGF-β, that are involved in new blood vessel growth.

Still, neither Swaroop nor Gorin is ready to give up on a possible role for *LOC387715* in AMD. "One has to do a lot more work to demonstrate that a SNP is associated with causality" and is not just a disease-gene marker, Swaroop says. But if the *HTRA1* link holds up, researchers will have a new route to explore as they attempt to understand—and develop better diagnostic methods and therapies for—wet AMD.

–JEAN MARX

SCIENTIFIC PUBLISHING

MEDLINE Supplements Must List Corporate Ties

Stepping into the fray over conflicts of interest in biomedicine, the National Library of Medicine's (NLM's) MEDLINE abstracts database will soon begin barring journal supplements that don't include financial disclosure statements.

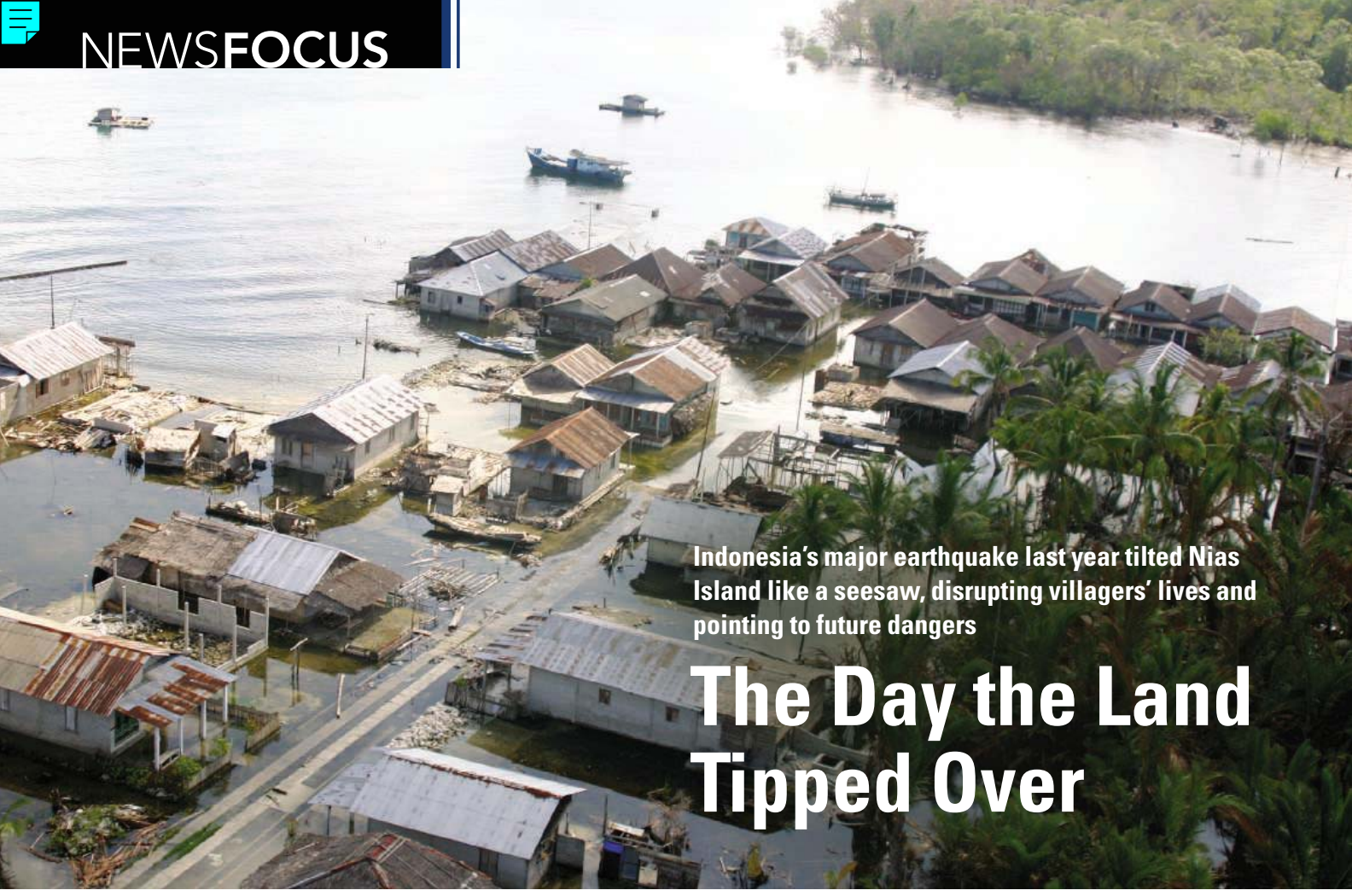
At issue are special volumes that often focus on a specific topic. James Marcetich, head of the MEDLINE index section, says NLM noticed in the past year that of the 1500 or so supplements processed each year, about 4% of all 2005 journal issues, a growing number were funded by drug companies but did not disclose that the companies had paid some authors to write articles about their products. "It just left a terrible impression," he says.

When the new policy goes into effect in January 2007, supplements will have to describe authors' relevant corporate ties or else they won't be listed. NLM is even including nonprofit sponsors after the watchdog group Center for Science in the Public Interest (CSPI) complained this month that a June supplement on dietary salt in the *Journal of the American College of Nutrition* lacked disclosures. The issue was paid for by a nonprofit that gets much of its funding from companies.

Meanwhile, CSPI's Merrill Goozner says he's pondering whether to ask NLM to extend the policy to all articles and to note disclosures in abstracts. Marcetich questions whether that's necessary, noting that regular journals are already screened for quality—including disclosure policies—before they're listed in MEDLINE.

–JOCELYN KAISER

CREDIT: A. DEWAN *ET AL.*, *SCIENCE*

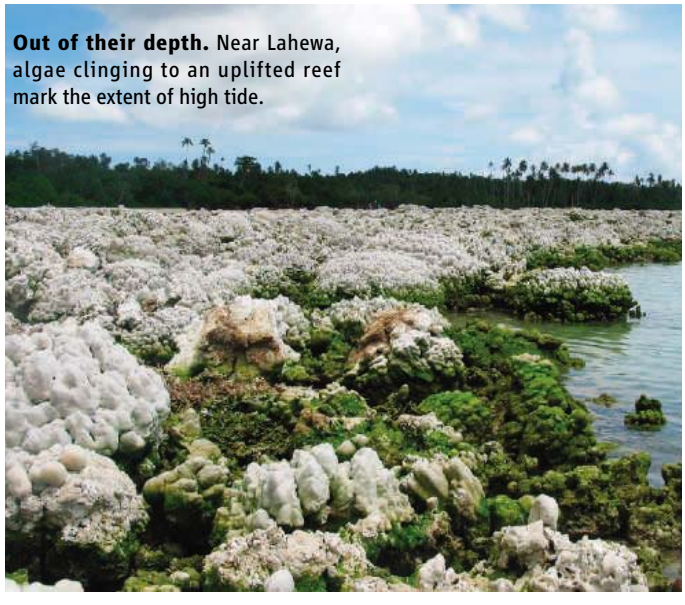


Indonesia's major earthquake last year tilted Nias Island like a seesaw, disrupting villagers' lives and pointing to future dangers

The Day the Land Tipped Over

NIAS, INDONESIA—Jolted awake late in the night of 28 March 2005, Ahmad Chatib staggered outdoors to find fissures in the ground snaking from the beach up to his wooden house. He and others in Tagaulei, a seaside village on Nias Island off Sumatra's west coast, didn't hesitate. "We took our children and ran," says Chatib, a former village head. Fresh in memory was the tsunami that 3 months earlier had claimed more than 160,000 lives in Sumatra's Aceh Province, 500 kilometers to the north. Of Tagaulei's couple of hundred residents, all but four—two mothers with infants who moved too slowly—escaped. Within an hour, most homes had been swallowed by the sea.

It wasn't a tsunami that wiped Tagaulei off the map but subsidence caused by a rupture of the Sunda megathrust, the subduction zone that parallels Sumatra's west coast, 25 kilometers below the village. The great 2005 Nias-Simeulue fault break, which generated an earthquake with a magnitude of 8.7, instantly yanked down Nias's southeast shore some 30 centimeters. The earthquake's sustained shaking then made vast stretches of beach liquefy and spread, lowering the coast by another meter or more in places and leading to the inundation of buildings during high tide. Erosion since the quake has erased most vestiges of the once-picturesque village. On Nias and nearby islands, "places with minor subsidence are being massively rearranged," says Richard Briggs, a geologist at the California Institute of Technology in Pasadena and member of a Caltech–Indonesian Institute of Sciences (LIPI) team that has spent a decade probing the region's tectonics.



Out of their depth. Near Lahewa, algae clinging to an uplifted reef mark the extent of high tide.

While the quake lowered southeast Nias, it lifted parts of the island's northwest coast nearly 3 meters, thrusting coral reefs into the air and extending the shoreline by hundreds of meters in places. Although such upheavals go hand in hand with a major earthquake of this kind, the Caltech-LIPI team, led by paleoseismologist Kerry Sieh, has used painstaking geodetic measurements to put together one of the finest-grained maps of seismic deformation. The portrait of Nias reveals in unprecedented detail how subsidence and uplift can utterly remake a landscape. "The ecological changes are profound," Briggs says.

The severe warping of Nias offers an unsettling preview of what may await central Sumatra's

CREDITS (TOP TO BOTTOM): KERRY SIEH AND ARON MELTZNER; DANNY HILMAN NATAWIDJAJA

Sunken city. Villagers in Haloban, on Tuangku, one of the Banyak Islands, must cope with daily flooding.

west coast, including the major city of Padang. It faces a segment of the Sunda megathrust that the Caltech-LIPI team says is likely to rupture within the next few decades (see sidebar, p. 408). If a massive slip does occur, models suggest that the coastline around Padang would subside tens of centimeters, in a reprise of the devastation in Banda Aceh, which subsided by an average of 50 centimeters during the 2004 earthquake. Faced with that bleak outlook, Indonesian authorities must assess the feasibility of girding coastal structures against the subsidence and uplift of future megaquakes, says Danny Hilman Natawidjaja, a geologist at LIPI's Research Center for Geotechnology in Bandung. "It's important, absolutely, to do this," he says.

The social consequences of the 2005 catastrophe for islanders whose homes straddle the Sunda megathrust will take years to overcome. The region's economy lies in tatters. On Nias, patchy reconstruction efforts have left Chatib's family and hundreds of others living in tents and other temporary shelters. In the nearby Banyak Islands, only a few kilometers from the quake's epicenter, primary, or tectonic subsidence during the earthquake pulled the land down as much as a meter in some areas. There, to compensate for regular flooding, villagers have built elevated wooden walkways, as in Venice, and retreat to upper floors when the water creeps in. "I'm not sure that we in the West would put up with this for long," says Briggs.

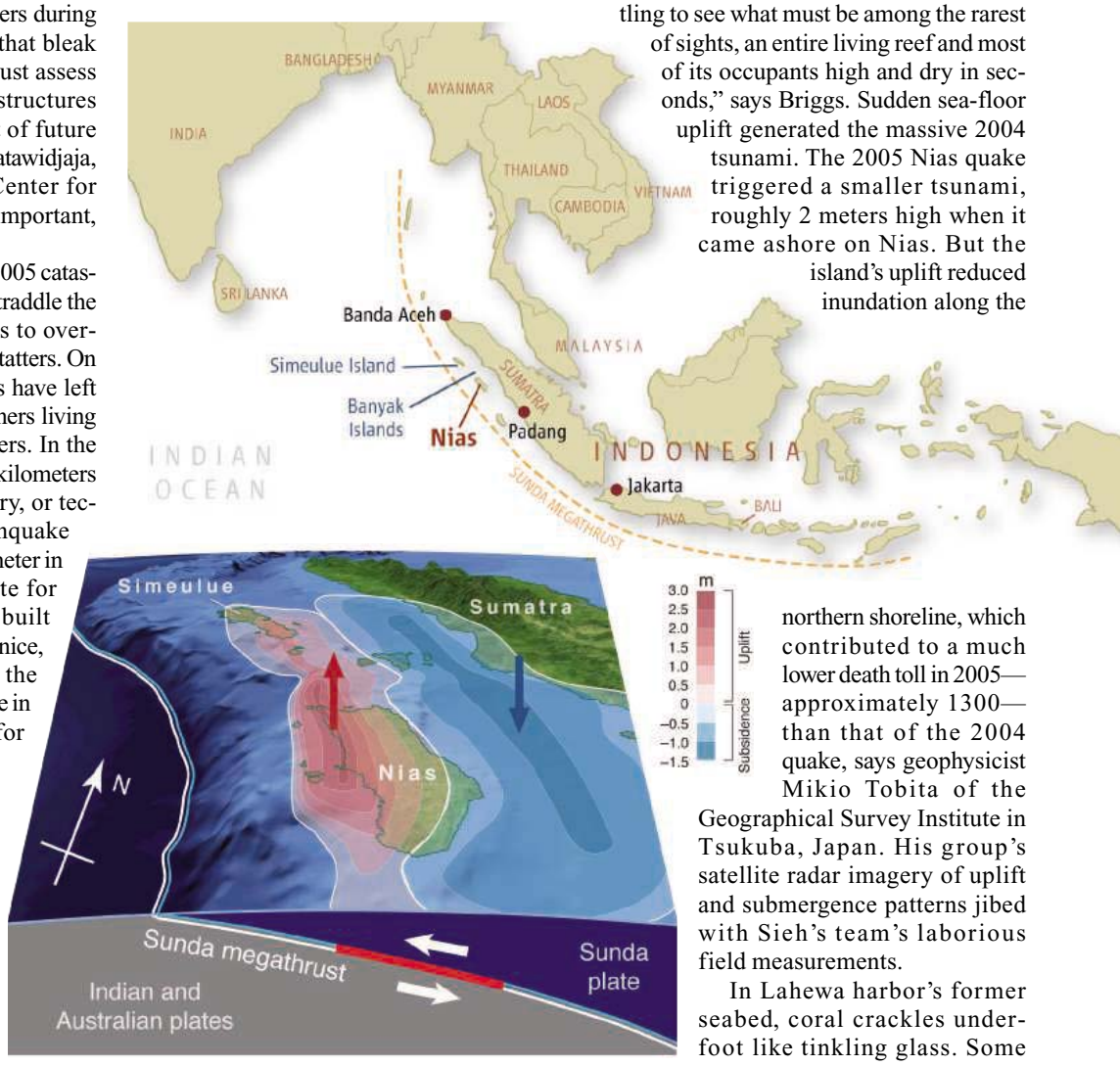
Vanished mangroves

On a wet September morning, the 3-hour drive by minivan from Nias's main town, Gunung Sitoli, to the northwestern port of Lahewa winds across hills verdant with coconut palms, banana trees, and cocoa trees from which mottled yellow, tear-shaped pods hang like Christmas tree ornaments. It's also a trail of tears. The 2005 earthquake, which released more than a century of pent-up strain in the subduction zone, leveled many homes and rearranged aquifers, causing some wells and rivers to run dry. Problems with water supply in coastal areas are "widespread," says Briggs, who has chronicled deformation of the altered landscape.

Electricity was out for 3 months, according to Ahmad Yani, a businessman from Gunung Sitoli. After power was restored, it took a couple more months for Nias's survivors, wearing surgical masks against the stench of rotting flesh, to clear the rubble. All the while, powerful aftershocks terrified many into believing that Nias would just sink and disappear. "A lot of people fled the island," says Yani.

A few kilometers east of Lahewa, the road bends around a wide, sandy beach. "Before the earthquake, this was all mangroves," says Imam Suprihanto, an independent marine biologist and divemaster based in Jakarta who collaborates with the Caltech-LIPI team. Now the beach is bare; the mangrove forest, which had helped prevent erosion and shelter wetland creatures, was wiped out by an uplift of roughly 2 meters, and the shore these days extends several hundred meters farther toward the sea than it did before the earthquake tilted the land. Megaquakes in the region have wreaked similar havoc before. Measurements show that the Mentawai Islands off the coast of Padang rose 0.8 meter in 1797 and 2.8 meters in 1833, says Mohamed Chlieh, a geodynamic modeler at Caltech.

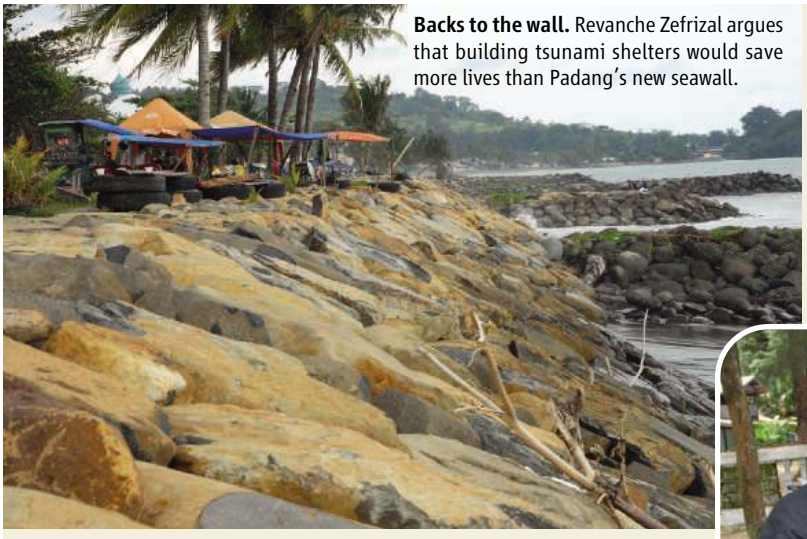
Some residents of Lahewa lost their livelihoods as well as their homes. The uplift transformed the harbor and surrounding beaches into an otherworldly vista of exposed coral reef colored in somber shades. "It must have been amazing and startling to see what must be among the rarest of sights, an entire living reef and most of its occupants high and dry in seconds," says Briggs. Sudden sea-floor uplift generated the massive 2004 tsunami. The 2005 Nias quake triggered a smaller tsunami, roughly 2 meters high when it came ashore on Nias. But the island's uplift reduced inundation along the northern shoreline, which contributed to a much lower death toll in 2005—approximately 1300—than that of the 2004 quake, says geophysicist Mikio Tobita of the Geographical Survey Institute in Tsukuba, Japan. His group's satellite radar imagery of uplift and submergence patterns jibed with Sieh's team's laborious field measurements.



Seismic shift. When a 400-kilometer-long stretch of the Sunda megathrust ruptured on 28 March 2005, the slip yanked down eastern Nias while thrusting up the island's west coast.

In Lahewa harbor's former seabed, coral crackles underfoot like tinkling glass. Some microatolls of the coral genus *Porites* are taller than a minivan; the Caltech team zeroed in on these as records of uplift in 2005 and earlier quakes (*Science*, 31 March, p. 1897). Where fishing boats were once moored, hermit crabs and mudskippers skitter in their tidal pools. The earthquake shrugged a concrete jetty off its pillars, which now jut at odd angles. In the days after the quake, waves pulverized the beached fishing boats. Only a few larger vessels at sea escaped intact.

CREDIT (BOTTOM): R. BRIGGS/CALTECH; OBLIQUE SHADED RELIEF: NASA WORLD WIND/BLUE MARBLE; ILLUSTRATION: A. STONEBRAKER/*SCIENCE*



Backs to the wall. Revanche Zefrizal argues that building tsunami shelters would save more lives than Padang's new seawall.

Facing a Tsunami With No Place to Run

PADANG, INDONESIA—It is hard to imagine a more terrible catastrophe than the 2004 tsunami that killed more than 220,000 people in southern Asia. But experts say that the next great earthquake on the Sunda trench could be at least as bad. Geologists warn that within the next 30 years, there will likely be another great Sunda megathrust rupture farther south, just off Padang, Sumatra's second largest city, where 800,000 people live. "We're getting close. Strain has been accumulating for more than 200 years," says Richard Briggs, a geologist at the California Institute of Technology (Caltech) in Pasadena. "The outlook isn't promising."

Even knowing this, planners are struggling to devise an adequate evacuation plan. If the megathrust rupture occurs where it's expected, offshore of Padang, people will have a mere 20 to 30 minutes to reach a safe haven before the resulting tsunami hits. The city's diabolical geography and street grid, hard up against the volcanic Barisan Mountains and criss-crossed with rivers and swamps, make it impossible for the entire population to flee, says Revanche Zefrizal, a coordinator for the nonprofit Komunitas Siaga Tsunami (Kogami). "We have five death zones," says Zefrizal, making a throat-slitting gesture. He and others are stumped on how to get 200,000 people near the seafront to safety in time. "We haven't overcome this challenge yet."

It's not for lack of trying. Zefrizal, with the Indonesian military, local police, and emergency services personnel, has been staging evacuation drills and school education campaigns district by district in the Padang region. Meanwhile, a German-Indonesian team has deployed sensors off the coast to measure sea-floor vibrations and pressure changes in the water column that could alert the mainland within tens of seconds of an oncoming tsunami. But they are still working out the kinks. "We can't wait for the technology," which might fail in a crisis, says Harmin Rauf, head of Satkorlak PPB, Padang city's disaster-mitigation office. Therefore, he says, early recognition of a tsunami-spawning earthquake is essential.

With that in mind, Kogami has been instructing locals to be prepared to act decisively if tremors last more than a minute and are so strong that they fell building supports and knock people off their feet. In that event, Zefrizal says, quake survivors must pick themselves up and flee on foot to high ground or take shelter in the upper floors of designated tall buildings that withstand the quake. "People wouldn't have time to go looking for mothers or their children. They have to just run," says Rauf. He's working

The destruction of the harbor was a cruel blow. At a fish market once lapped by the harbor's waters but now several hundred meters inland, sales have been dismal. Relief agencies donated replacement boats, but most fishers have taken construction jobs, says Syaharfani Aceh, a fisher. And those who still fish "are afraid to go far out to sea," he says, because uplifted corals just below the surface, most yet to be charted, pose a navigation hazard. Before the earthquake, fishers tended to put to sea at night, when catches are greater. So pervasive is the fear of another quake, Aceh says, that now they are afraid to leave their families alone after dark. And even moving the diminished stock is hard. "It's like the disaster just never stops for the fishermen and their families," says Briggs.

An endurance test

The earthquake destroyed the road to Tagaulei, so the only way to reach it now is by a half-hour ride in a skiff from Bozihona, a village up the coast. Several beachfront homes in Bozihona, which also subsided, are half-buried in muck and sand. But its easier access allowed the Association of Medical Doctors of Asia (AMDA) to quickly erect 30 replacement homes here last July.

Uncertain future. Ahmad Chatib lost his home and his boat to subsidence.

Approaching Tagaulei's new beach, the boatman cuts his engine, and the skiff drifts past a few dark, wooden posts poking above the waves—all that remains of beachfront homes. As the skiff is hauled ashore, a shirtless man in his 30s ambles over. Arman Aceh, a former fisher, points out to sea at a wall-less house frame sticking up from the waves—the only structure still with a roof. "That's my home," says Aceh, teeth stained orange from a mix of areca nut and chalk, wrapped in betel leaf, bulging inside his cheek. He says there were houses even closer to the pre-earthquake shoreline, about 300 meters out to sea from the present one; they have vanished.

Joining the conversation on the beach at Tagaulei is Chatib, a long *balatu* blade hanging, sheathed, from his belt. He points to lumber on a white tarp with the logo of the U.N. High Commissioner for Refugees. "The wood has been there more than a year," Chatib grumbles. "It's just rot-

CREDITS: R. STONE/SCIENCE

with the mosques to connect muezzin loudspeakers to a central radio dispatch for broadcasting warnings and instructions.

About 400,000 of Padang's residents live on the beach or in a warren of narrow streets along the coast. Two- and three-story apartment complexes, shops, and restaurants are interspersed with striking buildings with sharply sloping roofs: "bull's horns" symbolizing the bravery and resilience of the Minang people of west Sumatra. Close to shore, not even the imposing Minang architecture could stave off a tsunami. "All these buildings would be swept away," says Imam Suprihanto, a marine biologist who works with the Caltech team. The city has laid down boulders to form a 5-meter-high seawall, "but this will only protect Padang from a small tsunami," Rauf says. The towering waves from a great quake would wash over them. Only a few main roads lead inland, leaving about half of the beachside residents no viable escape route.

City officials plan to widen the main roads, says Rauf. Another idea is to build a series of concrete towers along the beach in which people stranded near shore could ride out a tsunami. One prominent advocate of this approach is Roger Bilham, a geophysicist at the University of Colorado, Boulder, and a top expert on earthquake risk in Southeast Asia. "Tsunami shelters should be constructed every 100 meters along the coast," he says. Bilham envisions 10-meter-high "indestructible platforms" with numerous entry stairs and stocked with supplies. Zefrizal backs the idea, although at present there's a showstopper: "There's no money in the budget to make the towers," he says. Kogami plans to go cap in hand to international nonprofits.

The potential for severe subsidence would complicate tower construction and an evacuation. Just as the quake that shook southeastern Nias Island last year tilted the landscape (see main text), a Padang earthquake would be accompanied by subsidence along the coast, says Briggs. Modeling by Caltech's Mohamed Chlieh, based on the effects of megathrust ruptures off Padang in 1797 and 1833, predicts tectonic subsidence—a tugging down of the western Sumatran coast near Padang—of up to 50 centimeters, roughly the same as in Aceh Province, on Sumatra's northern tip, in 2004. Slumps and fissures from liquefaction of soft, sandy ground could exacerbate local flooding.

Modeling by Jose Borrero of the University of Southern California in Los Angeles has shown that subsidence will abet the killing power of a tsunami, allowing water to run farther inland with more energy, threatening about 1 million people along a 500-kilometer stretch of coast. Thus tsunami shelters would have to be built to ride out a stronger wave *and* shifting ground.

Psychology will also come into play. "West Sumatrans believe in science, but as Muslims, we also believe that natural disasters are God's will," says Rauf. "We want to know how to cope with a tsunami better. But we will not be afraid of it." Rauf can only hope that the rest of the population will be so levelheaded when the day of reckoning comes, as it surely will.

–R.S.

Flip-flop. Before the 2005 rupture, Nias's southwest coast was subsiding, as indicated by the stand of dead coconut palms seaward of the beach (*top*). The rupture lifted the coast here 2.5 meters.

ting." During the earthquake, the survivors ran inland about a kilometer to a settlement also called Tagaulei. Halfway to the second Tagaulei, a path through bamboo rushes passes a small clearing with plots for three homes, including one for Aceh's family. All that's been built so far is the concrete base. "We are waiting for our wood," Aceh says.

Before the earthquake, Chatib was a fisher. Now, sans boat, he says he has been reduced to selling fish caught by other men. "We are very poor," he says, before adding, bitterly, "Why are we still living like this? We feel left out and forgotten."

AMDA's senior logistics officer sympathizes with the Tagauleians' plight. "We feel very sorry for them. They have been waiting so long" for help, says Naoto Usami. AMDA chartered an amphibious craft last year to deliver the lumber now sitting on the beach; the nongovernmental organization didn't anticipate the difficulty of moving it inland to homesteads in Tagaulei Two. The delays have created tensions with the villagers. "Our staff have been threatened with knives," he says. AMDA is planning a second lumber shipment for next month and aims to complete all homes by the end of January. "Now," says Usami, "we're moving very fast."

Night has fallen, and Chatib says goodbye: a melodious "*Ya-ahowu!*" "*Yahowuuuuu!*" yodels Suprihanto, who does not speak the local language. Others chime in with mangled variations like off-key a cappella singers; it's infectious. The skiff sets out for the return to Bozihona. Lightning flares on the horizon. But the sea is glassy calm, and glowing bioluminescent plankton stream off the bow like sparks. The breathtaking serenity is a sharp contrast to the horrors that Chatib and his fellow villagers endured last year.

Over the coming decades, the tilted crust around Nias will settle gradually—returning to its approximate position before the 2005 quake—as strain on the fault builds to a crescendo for the next gargantuan release. But for Chatib and many other islanders, life may never regain its prequake equilibrium.

–RICHARD STONE

CREDITS: KERRY SIEH

CREDIT: NASA/SWIFT/S. IMMLER

Early Look at Exploding Supernova Spotlights Deadly Stellar Tango

A lucky glimpse of x-rays emanating from a stellar explosion may be good news for the reliability of cosmologists' favorite standard candle.

Astrophysicists using NASA's Swift satellite have spotted the first signs of x-rays produced in the aftermath of a type 1a supernova, a cataclysmic burst of energy used to gauge cosmic distances. Because all type 1a supernova explosions are supposedly produced by a common ignition mechanism, differences in their apparent brightness can be used to compute distances to far-off galaxies in which the explosions occur. Measurements of type 1a supernovae have provided the prime evidence that the universe is expanding at an accelerating rate.

The new results help confirm the standard picture of type 1a explosions, says Eric Schlegel of the University of Texas, San Antonio, who was not involved in the research. Cosmologists have assumed that type 1a supernovae occur in binary systems in which a white dwarf star about as massive as the sun grows by siphoning off material from a nearby companion. When the white dwarf swells to more than 1.4 times the sun's mass, it ignites in a thermonuclear explosion, blowing itself to bits.

But there was always a chance that the presumed scenario was naïve or mistaken. The new results are the strongest observational evidence so far confirming the standard picture. "Without knowing it was a white dwarf in a binary system, there was always that nagging worry that nature was more clever than we were," Schlegel says. "This helps eliminate that worry."

The findings support the white dwarf mechanism by establishing the existence of a companion, which would be necessary to provide a white dwarf with the excess matter needed to explode. The report also identifies the nature of the companion star, said Stefan Immler, the leader of the Swift team, who presented the results at the meeting. Immler, of NASA's Goddard Space Flight Center in Greenbelt, Maryland, said scientists have debated whether the companion is another white dwarf or a more massive star. The new data point to a more massive star, at least for this supernova, designated 2005ke. It was spotted last year in galaxy NGC 1371, about 65 million light-years away.

Detection of x-rays within days after the explosion indicates that its shock wave encountered dense gas near the supernova. That material must have blown in on the stellar wind from a massive companion star. Observations of ultraviolet radiation from the explosion, about a month later, also confirm that explanation, Immler said. Only a huge star could provide enough matter to account for the radiation produced.

Immler stresses that many more explosions will need to be observed over lengthy time periods to know for sure whether such explosions are really reliable standard candles for cosmological studies. "We're trying to get the big picture here," he says. "We're making a concerted effort to observe as many supernovae as we can as fast as we can."

A paper describing the new results was published last month in *Astrophysical Journal Letters*. **–TOM SIEGFRIED**

Tom Siegfried is a writer in Los Angeles, California.

Snapshots From The Meeting >>

Galactic jet fuel. In most galaxies, including our Milky Way, a supermassive black hole sits quietly at the core. But in a small subset of galaxies, the nucleus is "active," spewing energetic radiation. And in a still-smaller subset, some of the energy shoots into space in the form of bright beams known as jets.

For years, astronomers have wondered about what the jets are made of. Now there is an answer, based on two active galactic nuclei observed by NASA's Swift satellite.

Jets are known to contain electrons but are electrically neutral, so some positively charged particles—either protons or positrons—are needed to balance the electrons' negative charge. At the meeting, Rita Sambruna of NASA's Goddard Space Flight Center in Greenbelt, Maryland, reported that Swift measurements of x-rays produced in the jets indicate that they contain protons. The total amount of matter in a jet at any given time, Sambruna says, is about equivalent to the mass of Jupiter.

Black-hole dervish. The Japanese x-ray satellite Suzaku has pinned down the spin of a massive black hole in the core of galaxy MCG-6-30-15. Previous observations hinted that the black hole is spinning rapidly. Suzaku has verified those suspicions with precise measurements of x-rays emitted by hot gas near the black hole, Andrew Fabian of the University of Cambridge, U.K., reported at the meeting. The spinning rate is on the order of one rotation every 5 minutes, Fabian says, about 90% of the physically possible maximum.

Chris Reynolds, an astrophysicist at the University of Maryland, College Park, who was not involved in the research, says the finding is significant for confirming that some black holes spin so rapidly. As much as 30% of a black hole's energy can be stored in its rotational motion, Reynolds said, suggesting that the spin may contribute to the energy output of quasars, cosmic lighthouses believed to be powered by black holes at the core of active galaxies. **–T.S.**

PROFILE: HELAMAN FERGUSON

Carving His Own Unique Niche, In Symbols and Stone

By refusing to choose between mathematics and art, a self-described "misfit" has found the place where parallel careers meet

BALTIMORE, MARYLAND—Helaman Ferguson's sculpture studio is set back from the road, hidden behind a construction site. Inside, pieces of art line shelves and cover tabletops. Ferguson, clad in a yellow plastic apron and a black T-shirt, serenely makes his way through the room. The 66-year-old is tall and white-haired, his bare arms revealing a strength requisite for his avocation.

The most striking work in the studio is a more than 2-meter-tall, 5-ton chunk of granite. When it is finished, it will stand in the entry to the science building at Macalester College in St. Paul, Minnesota. Right now, it is a mass of curving surfaces sloping in different directions, its surface still jagged with the rough grains left by the diamond-toothed chainsaw Ferguson uses to carve through the stone.

"I'm in my negative-Gaussian-curvature phase," Ferguson says. "Say we're going to shake hands, but we don't quite touch. OK, see the space between the two hands?" That saddle-shaped void, he explains, is a perfect example of negative Gaussian curvature. Our bodies contain many others, he adds: the line between the first finger's knuckle and the wrist, for instance, and where the neck meets the shoulders.

The topological jargon is no surprise: Ferguson spent 17 years as a mathematics professor at Brigham Young University (BYU) in Provo, Utah. What is unusual is how successfully he has pursued a dual career as mathematician and artist and the ease with which he blurs the categories. Math inspires and figures in almost all of Ferguson's artistic works. Through them, he has helped some mathematicians appreciate the artist's craft and aesthetic. And he's persuaded perhaps even more artists that math may not be as frighteningly elusive as they believe, or even if it is out of their reach, it's as beautiful as any work of art they might imagine. "The way he has brought together the worlds of science and the arts—this is an admirable thing," says Harvey Bricker, Ferguson's former college roommate.

Function-al form. The Fibonacci Fountain at the Maryland Science and Technology Center was inspired by the "golden ratio."

CREDITS: J. MOGLIA/*SCIENCE*

Twin callings

Ferguson himself finds it hard to say which calling came first. As a teenager in upstate New York, he learned stone carving as an informal apprentice to his adopted father, a stonemason. Artistically, however, he was more drawn to painting. After finishing high school in 1958, he wanted to study art as well as math. He chose Hamilton College, a liberal arts school in upstate New York near where he had spent most of his childhood, where he could do both.

After getting his math degree, he enrolled in a doctoral program in math at the University of Wisconsin, Madison. He paid for some of his living expenses by selling paintings. He also met and began dating an undergraduate art student, Claire. The couple married in 1963 and had their first child (of an eventual seven) in 1964. Ferguson dropped out of school for a couple of years to work as a computer programmer, then resumed his math studies. He obtained his master's degree in mathematics at BYU and a doctorate in group representations—a broad area of math that involves algebra, geometry, topology, and analysis—at the University of Washington, Seattle. In 1971, he accepted an appointment as assistant professor at BYU.

As a mathematician, Ferguson is perhaps best known for the algorithm he developed with BYU colleague Rodney Forcade. The algorithm, called PSLQ, finds mathematical relations among seemingly unrelated real numbers. Among many other applications, PSLQ provided an efficient way of computing isolated digits within pi and blazed a path for modeling hard-to-calculate particle interactions in quantum physics. In 2000, the journal *Computing in Science and Engineering* named it one of the top 10 algorithms of the 20th century.

Meanwhile, Ferguson's artistic career also developed apace. When he married Claire, a painter, the two struck a deal: "I get the floors, she gets the walls," he says. He began focusing more on sculpture. The art department at BYU allotted him some studio space, and he turned out a regular stream of work. He's done commissions for the Maryland Science and Technology Center, the University of California, Berkeley, the University of

St. Thomas in St. Paul, and many other institutions. He has also designed small sculptures for awards presented by the Clay Mathematics Institute in Cambridge, Massachusetts, the Canadian Mathematical Society in Ontario, and the Association for Computing Machinery in New York City.

He has worked to keep a foot in each of the "two cultures." While at BYU, he taught a course each year for honors students called Qualitative Mathematics and Its Aesthetics. Both art students and math students enrolled: the artists looking for a palatable way to take in a math requirement, and the math students lured by the promise of higher level mathematics. Ferguson delivered on both ends. He taught concepts mathematicians don't normally encounter until graduate school, such as braid theory. Artists could relate to braids as physical objects, rope or hair that can be woven into a specific form. But students were also asked to write down an algebra to go along with how the braid was formed—a noncommutative algebra.

"Some of these folks were in there because they were either afraid of or hated math," says Ferguson. At the end of the semester, however, "quite a few art students wanted a follow-on semester—more math, more art."

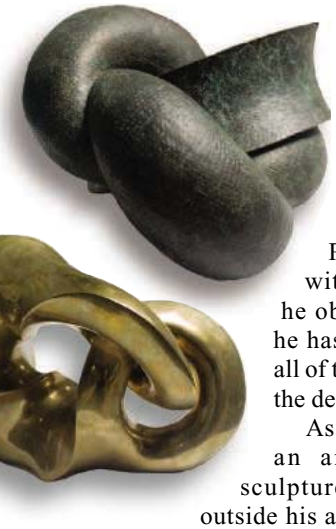
Bridging

Ferguson, who left BYU in 1988, now devotes most of his time to his art. For his large-scale or complicated pieces, he uses computer programs such as Mathematica to form and refine the shape he wants the finished piece to take. "With sculpture, you want a piece to be a unit so it has direct impact as a form," he says. "Sculptures are complicated enough already." With computer programs, he says, before even putting hand to stone "you can walk around [the piece] and see a different view; you can touch it and reshape it to make it simpler and more direct."

Once the design is in place, Ferguson turns to the task of carving the stone. He works alone, without assistants, using both chisels and assorted power tools. Finally comes a lengthy smoothing process, going from 20-grit sandpaper to as fine as 8500-grit. Ferguson has to work "wet" much of the time, using water to wash down the fine particles of stone that could otherwise become deposited in his lungs. For some of the work, he dons gloves made of woven stainless steel and a positive-pressure facemask. A large sculpture can take several months to complete, working flat-out.

Granite is Ferguson's favorite medium. "Mathematics is kind of timeless," he says, "so incorporating mathematical themes and ideas into geologically old stone—that's something that has great aesthetic appeal to me." He also likes the idea that his sculptures will be around for millions or even billions of years.

The finished sculptures vary widely in appearance. Some are delicate, with looped projections or intricate imprints, and are small enough to hold in one's hand. Others are massive, meant to be touched, even climbed on (as many children have discovered). As a rule, they also contain much more detail than meets the eye. "My work generally involves a circle of ideas," says Ferguson. People he interacts with, new information he obtains, mathematics he has had on his mind—all of these become "part of the design consideration."



Twisted. Braids and knots turn up in many of Ferguson's works, including these small metal sculptures

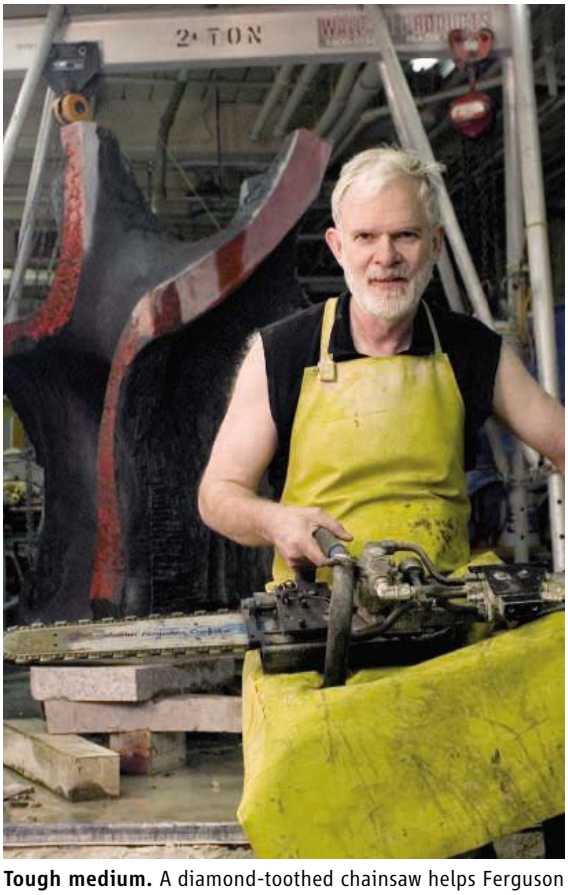
As an example, he cites an architectural-scale sculpture recently installed outside his alma mater Hamilton College's new science building. The work, made of 10-centimeter-thick granite, centers on a pair of massive disks representing the planets Mars and Venus. "Venus" is exactly 161 centimeters in diameter—the height of the average female Hamilton student, taken from the records of one of the college's psychology professors. "Mars" is 174 centimeters in diameter—the average male student's height. The disks are inlaid with tiles in a pattern defined by the Poincaré and Beltrami-Klein models of plane hyperbolic geometry.

Ferguson's admirers say his artwork goes far beyond academic exercises. David Broadhurst, a physicist at the Open University in Milton Keynes, U.K., learned about Ferguson's sculpture after using the PSLQ algorithm in his research in quantum mechanics. He compares Ferguson's artistic renderings of math to Fournier playing the Bach cello suites, "giving expression to abstract forms, whose beauty is preexistent to the interpretation, yet recreated in a widely accessible medium."

For his part, Ferguson says his lifelong project to embody mathematics in mass and form is very much in the spirit of the times—and he credits technology with making it all possible. "We're living in the golden age of art, we really are. But it's also the golden age of science," he says. "Today, young people have seen more art and science in, say, their first 25 years of life than anyone in the years before that." With the collaborations between computer scientists and artists, and tools for art being used as tools for scientific exploration and invention, Ferguson suggests we may be in the midst of a second Renaissance. "It's a great time to be alive," says Ferguson, "because there are more places for misfits like myself to survive."

–KATHERINE UNGER

Katherine Unger is a writer in Washington, D.C.



Tough medium. A diamond-toothed chainsaw helps Ferguson carve through granite rocks that are up to a billion years old.

CREDITS: J. MOGLIA/*SCIENCE*

Invest in Italy

ITALIAN BIOTECH is gaining momentum

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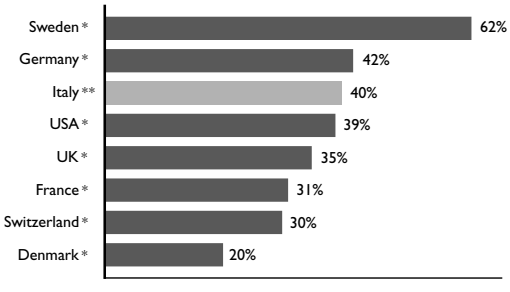
Innovation in Life Sciences Companies: R&D Spending/Revenues *(%)*



Source: InvestInItaly based on:

* Critical I "Biotechnology in Europe 2005 Comparative Study"

** Blossom Associati, CrESIT Insubria di Varese University, Italian Biotechnology Report 2006

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ITALIAN BIOTECH DATABASE

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Innovation Spotlight

Italy's just launched the first public laboratory for production of personalized anti-cancer drugs for clinical trials

Rome – FaBioCell (Cellular Biological Pharmaceuticals) is the new public laboratory inaugurated by the Italian Minister of Health. Located in the ISS (the Italian National Institute of Health) it will use the dendritic cells of individual patients for the production of anti-cancer drugs and vaccines. It will allow trials of cancer immunotherapy, in collaboration with 3 major Italian hospital centers: Istituto Regina Elena of Rome, Institute for Cancer Research and Treatment (Fondazione G. Pascale of Naples) and the National Cancer Institute of Milan.

Italy to Launch Europe's First Institute for Regenerative Medicine

Modena – The University of Modena and the Eye Bank Foundation of Venice have joined forces to create a public/private partnership forming the Research Center for Regenerative Medicine. It will become the first such center in Europe focused on stem cell therapy for treating vision disorders caused by tissue/organ damage and genetic defects.

The European Institute of Oncology is supported by the US National Cancer Institute for lung cancer research

Milan – The Italy based European Institute of Oncology was selected and funded 850,000 USD by the National Cancer Institute as the best research center in Europe and US to conduct clinical studies for pharmacological prevention related to lung cancer. The research pool is committed to cancer screening with the ultimate and ambitious goal of discovering how to stop lung cancer growth at a very early stage.

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EDITED BY YUDHIJIT BHATTACHARJEE

Awards

DOUBLE CREDIT. Cell biologist Elizabeth Blackburn, who made headlines 2 years ago when she was dismissed from the President's Council on Bioethics, has won the $250,000 genetics prize from the Peter Gruber Foundation. The 57-year-old professor at the University of California, San Francisco, received the award last week for her scientific work as well as her opposition to the politicization of science.

In the 1970s, Blackburn and her colleagues discovered an enzyme called telomerase, which repairs the ends of chromosomes and keeps cells young and dividing. The finding has helped researchers understand how normal cells become cancerous. But Blackburn earned wider publicity in 2004 when she spoke out against what she perceived as the council's bias against embryonic stem cell research. As a result, she was not reappointed at the end of her 2-year term. "The emphasis [of the council's reports] was not balancing science as we knew it," she says, noting that the problem exists in many areas of science policy today.

Cancer biologist Thomas Cech, who heads the Howard Hughes Medical Institute in Chevy Chase, Maryland, says Blackburn's outspokenness "showed a lot of courage and strength of character."

NEW IOM MEMBERS. The Institute of Medicine (IOM) last week named 65 new members, taking its total membership to 1501. It also named five new foreign associates, which takes its total number in that category to 82. The list of the new inductees is at national-academies.org/morenews/20061009.html.

CREDITS (TOP TO BOTTOM): SOURCE: KIM KULISH/CORBIS; LOWELL/IMAGE: PHOTOS.COM

Got a tip for this page? E-mail people@aaas.org

DEATHS

EXPLORER. Philanthropist, yachtsman, and Lands' End mail-order empire builder Gary Comer, 78, died 4 October at his Chicago, Illinois, home after a long battle with prostate cancer.

In addition to donating tens of millions of dollars to bolster his boyhood working-class neighborhood of South Chicago, Comer became the leading funder of scientific research on abrupt climate change (*Science*, 24 February, p. 1088). "He's an explorer," said friend Philip Conkling of the Island Institute in Rockland, Maine, who noted that Comer's trip through the legendary Northwest Passage "transformed his life. He determined to understand from a scientifically rigorous point of view what was happening in the Arctic."

Comer's climate science largess totals some $35 million, half of which went toward a geochemistry building on the campus of Lamont-Doherty Earth Observatory in Palisades, New York, that was dedicated a week before he died.

MISCONDUCT

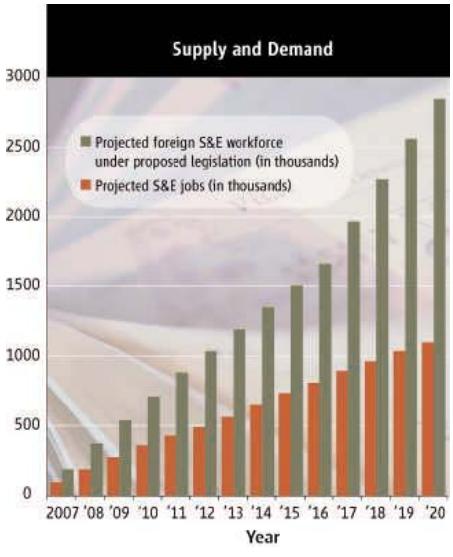
DISSERTATION BLUES. A Seoul National University (SNU) panel has concluded that four former members of the research team of now-disgraced Korean cloning scientist Woo-Suk Hwang committed misconduct while writing their doctoral theses.

The panel examined the theses of nine SNU veterinary school graduates who worked with Hwang. Yang Kuk, head of SNU's Office of Research, says one student replaced a photo of a somatic cell of a Korean beef cow with a somatic cell photo of a Holstein dairy cow. Another used photos of a pregnant cloned pig instead of the claimed ultrasound photos of a pregnant tiger. In the other two instances, Kuk says students used data or photos from papers authored by other people without properly citing them.

Kuk says that Hwang most likely did not know of these activities. The panel plans to recommend disciplinary measures that could include retracting or revising the theses.

Data Point >>

MORE ASHORE? How many foreign scientists and engineers would enter the U.S. workforce if the immigration bill passed by the Senate in May became law? Over a 10-year period, five times the number allowed under current rules, says B. Lindsay Lowell, a demographer at Georgetown University in Washington, D.C., who worked out the estimate for the Institute of Electrical and Electronics Engineers–USA (IEEE-USA).

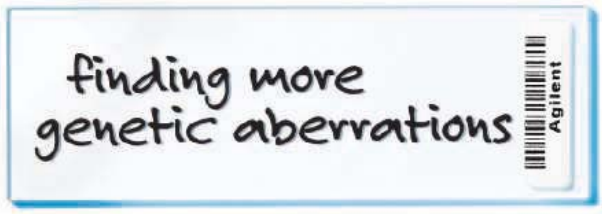


The estimate* is based on the impact of Senate provisions, such as the granting of automatic green cards to foreign students earning U.S. graduate degrees in science and engineering (S&E). Those provisions, the study shows, would let 1.9 million more foreign S&E professionals into the country by 2017—far more than the 355,000 expected to join the workforce under current law.

That number far exceeds the projected demand for S&E workers in the American economy by 2017 as estimated by the U.S. Bureau of Labor Statistics, Lowell notes (see graph). Many, including Lowell, expect that the Senate bill will never become law because of House opposition.

*www12.georgetown.edu/sfs/isim/Publications/LindsayPubs/Lowell-Projections.pdf

Open to



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LETTERS

edited by Etta Kavanagh

HIV Testing and Individual Rights

IN THEIR POLICY FORUM "HIV TESTING IN CHINA" (9 JUNE, P. 1475), Z. WU *ET AL.* DESCRIBE THE new Chinese national program of active, provider-initiated HIV/AIDS testing among prisoners and other high-risk groups. For some groups, such as prisoners and government workers, individuals consent to health examinations that include an HIV test, rather than directly consenting to the test itself. As the authors admit, this strategy places community protection over individual rights. Although for some, routine HIV testing represents a standard public health response to a deadly epidemic, for others, this represents a dramatic reduction of individual control over when and how one is tested for HIV.

It seems likely that more aggressive HIV testing policies will be increasingly implemented globally as time progresses. Botswana and Lesotho have already initiated routine "opt-out" testing, whereby an individual must specifically request to not be tested (*1*, *2*). This strategy is now being promoted in the United States and South Africa (*3*, *4*). The new campaigns for testing are based on the premise that knowing one's status will reduce further infections and allow individuals access to treatment. However, for most people in low- and middle-income countries, no treatment is available and HIV-related stigma remains a reality. One can wonder what the next step will be if routine HIV testing policies do not make a large impact on the epidemic. Some already advocate mandatory testing in high-prevalence settings (*5*). Is the trend toward routine testing a transitional stage on the road to mandatory HIV testing?

Yijuan Duan, deputy director of Ruili CDC in Yunnan, takes a blood sample from a male drug user for HIV testing.

We should scrutinize the efforts and social context of individual countries before considering routine testing an acceptable custom. China, for example, has a history of illegal incarcerations and torture among prisoners, drug users, and sex workers (*6*). The "great fire wall" of China prevents the dissemination of HIV prevention strategies from Web sites catering to men who have sex with men (*6*). HIV/AIDS in China is still associated with widescale and, at times, authority-supported stigma (*6*). Governments have a responsibility to ensure that HIV testing does not discriminate against any person or group (*7*). Before we can accept routine testing among oppressed populations as public health leadership, we need nongovernmental evidence that these groups are benefiting from optimal health care options and that routine testing is not de facto mandatory testing with strongly adverse consequences for HIV-positive persons.

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Response

WE SHARE THE CONCERN EXPRESSED BY Mills and Rennie that human rights be respected in the midst of this terrible epidemic, both those of the HIV-infected and those of the HIV-uninfected.

The debate on whether to widely implement HIV testing has been gaining momentum in recent months, particularly because of the U.S. Centers for Disease Control's proposal to remove the need for pre-test counseling in light of available treatments (*1*–*3*). Because 25% of the estimated 850,000 persons infected in the United States (and much higher proportions worldwide) are unaware they are HIV-positive, the epidemic is driven by infected persons unaware of their status. In China, as a result of routine HIV testing between July 2005 and June 2006, 33,318 persons now know that they are infected with HIV and can both prevent infecting others and access treatment for themselves.

Routine testing requires that the individual actively refuse testing and may thus be considered by some as coercive (*2*) and as violating human rights. However, it is important to also consider the human rights of those being infected by persons who do not know their HIV status and to remember that the primary responsibility of public health professionals is to protect the uninfected (who are the majority of the population) while doing as little harm as possible to those who are already infected. This approach will minimize the impact of the epidemic on society as a whole. For example, it was argued that the rights of an unborn child were violated if its mother refused HIV testing and therefore denied her child access to treatment. Thus, routine testing of pregnant women was introduced in some states in the United States (*2*). As Mills and Rennie have correctly pointed out, the social context needs to be taken into account.

In Botswana, where routine "opt-out" testing has been in place since 2004, public support for the strategy is high, with one

CREDIT: RUILI CDC

study reporting that 81% of 1251 people surveyed were extremely or very much in favor of routine testing and a further 8.4% indicating they were somewhat in favor (*4*). China, like Botswana, has introduced a policy of free access to antiretroviral treatment, which is a strong incentive for accepting testing (*5*). Recent legislation in China also guarantees people living with HIV/AIDS their rights to employment, education, and marriage as well as health care, including HIV treatment (*6*).

HIV testing is an important component of prevention, but it is not being championed as the only means of prevention in China—nor should it be anywhere. Behavioral and harm reduction interventions among high-risk groups are in place and are being rapidly scaled up, as are programs to combat stigma against those with HIV (*7*). This includes men who have sex with men, for whom there are a number of online resources, some of which are government supported (*8*), and whose perspective and issues have been discussed during prime-time television on China's biggest national network (*9*, *10*). China has taken bold steps to reverse its prior attitudes and to stop HIV/AIDS. The international community should applaud this dramatic step forward and not dwell on past issues.

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

9. China Central Television Network, http://www.cctv.com/health/topic/health/UNAIDS/20050303/100612.shtml (2006).
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Operational Hurricane Intensity Forecasting

THE ARTICLE "A HURRICANE'S PUNCH STILL knocks out forecasters" (E. Kintisch, News of the Week, 1 Sept., p. 1221) describes conclusions reached in a report submitted to the Science Advisory Board of the National Oceanographic and Atmospheric Administration (NOAA) by a Hurricane Intensity Research Working Group. As noted in the article, a major conclusion of this report was the perceived need for high-resolution numerical modeling (with grid sizes as fine as 1 km) to ensure accurate forecasts of hurricane intensity. However, the Working Group also submitted a minority report, written by the present authors.

We have concluded that adoption of some prominent recommendations in the majority report will perpetuate a narrow focus on highly detailed computer simulation. That focus is incommensurate with both available NOAA in-house numerical-analysis support staff and available in-house computing power. It also presumes a detailed level of understanding of many phenomena that does not exist. The strong emphasis in the majority report on highly detailed computer simulation, and the need for greatly enhanced computer resources, obscure the fact that existing NOAA computational facilities are substantial by international civil-sector standards. Furthermore, NOAA's commitment of resources for further expansion of those computational facilities is impressive, within the constraints of the agency's overall budget. On the other hand, little attention is given to the possibility of using more traditional techniques of simplified analysis and numerical modeling (combined with laboratory experimentation), in conjunction with existing numerical models, to provide an alternative, rapidly executed aid for operational forecasters.

At the recent meeting of the Advisory Board, both reports were presented by John Snow, the Working Group Chairman. A motion to forward only the majority report was defeated, and the Advisory Board explicitly recommended that NOAA's Administrator consider both reports.

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The Danger of Mathematical Models

THE CONTROVERSY ENGENDERED BY STRING theory ("A 'landscape' too far?", T. Siegfried, News Focus, 11 Aug., p. 750) illustrates the dangers of assuming that mathematical models that seem to account for our real universe are in fact substantive and actually underlie the universe. String theory, by admitting mathematically the possibility of many universes including our own, suggests the relevance of an anthropic principle (which, as Siegfried writes, is used "to explain features of the universe by pointing out that had they been otherwise, life would be impossible"), which is objectionable to many physicists in that it is more a tautology than an explanation of anything. The universe we inhabit, and its operational principles, exist independently of our observation or understanding; mathematical models of the universe, and indeed mathematics itself, are descriptive tools that exist only in our minds. Mathematics is at root a formal description of orderliness, and since the universe is orderly (at least on scales of space-time and mass-energy, which are within our power to observe), it should come as no surprise that the real world is well modeled mathematically. The mistake comes in turning this relationship on its head and expecting that every sequela of a mathematical model enjoys some real-world counterpart. This is akin to believing in the abilities of a fortuneteller on the basis of a few correct predictions. In both instances, when vastly more than what is true or real is described, the occurrence of a description of real tidbits is neither remarkable nor significant. Significance arises when only that which is real is described. A mathematical model of reality that makes untestable predictions is not necessarily wrong, but it is irrelevant. Cosmology should stick to explaining that which has consequences for us, not that which cannot possibly do so.

KEITH BACKMAN

Bedford, MA, USA.

The "Source" of Drug-Resistant TB Outbreaks

MUCH HAS RECENTLY BEEN WRITTEN ABOUT extensively drug-resistant tuberculosis (XDR TB) outbreaks in South Africa ("Extensively drug-resistant TB gets foothold in South Africa," J. Cohen, News of the Week, 15 Sept., p. 1554). Although mono-, multi-, or

extreme drug resistance can be acquired in a strain of *Mycobacterium tuberculosis* through inappropriate therapy or poor compliance, this is arguably infrequent. In South Africa, XDR TB has been reported as an "outbreak," which implies transmission by definition. The real problem from a public health perspective, therefore, is to prevent transmission. Transmission can occur almost anywhere, and this problem is exacerbated in immune-compromised individuals. In much of the developing world, treatment relies on smear-based diagnosis followed by a standard regimen of first-line drugs and monitoring for sputum conversion at 2 to 3 months. In the absence of conversion, the patients are classified as possible resistance cases, and samples are sent for limited resistance testing (usually to the drugs isoniazid and rifampin only). Only if resistance to these is confirmed are further tests requested. Even then, testing is not routinely done for all antibiotics, so there can be a continuation of treatment with inappropriate antibiotics, ongoing transmission, and further acquisition of resistance. A proactive intervention is needed where the full spectrum of tests for all antibiotics are used at the outset. This is not generally part of most programs, partly because of the cost and difficulties involved. With the help of the local health authority and implementation of rapid molecular tests, we were able to stop a multidrug-resistant TB outbreak in the Cape Town environment by PCR-based genotyping of isolates and rapid intervention. Unless we accelerate diagnosis, we will not defeat TB.

PAUL D. VAN HELDEN, TOMMIE VICTOR, ROBIN M. WARREN

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TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Stability via Asynchrony in *Drosophila* Metapopulations with Low Migration Rates"

Esa Ranta and Veijo Kaitala

Dey and Joshi (Reports, 21 April 2006, p. 434) studied replicate laboratory populations of *Drosophila* and reported that low migration led to asynchrony among subpopulations. We argue that this unexpected outcome may be due to variation in the initial size of the subpopulations and uncontrolled stochasticity in the experiments.

Full text at www.sciencemag.org/cgi/content/full/314/5798/420a

RESPONSE TO COMMENT ON "Stability via Asynchrony in *Drosophila* Metapopulations with Low Migration Rates"

Sutirth Dey and Amitabh Joshi

Ranta and Kaitala find asynchrony in our experiment unexpected and suggest stochasticity as a possible causal mechanism using simulated two-patch metapopulations. However, their mechanism can yield either subpopulation synchrony or asynchrony. We extend their approach to a nine-patch system approximating our experiment and show that asynchrony is not only not unexpected but extremely likely in real metapopulations with low migration.

Full text at www.sciencemag.org/cgi/content/full/314/5798/420b

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SCIENCE AND SOCIETY

Biotechnology and the Human Soul

Michael A. Goldman

I never read Lee Silver's *Remaking Eden* (*1*). I found the author's bravado in interviews as an unabashed salesperson for our biotechnological future distasteful and embarrassing. I almost dropped a popular textbook just for adding him as a co-author. I still cringe a bit after reading *Challenging Nature*, but now I think it isn't so bad to have an eloquent, well-traveled, and well-read counterbalance for Leon Kass and Jeremy Rifkin. It is refreshing to see Silver's careful, though biased, examination of the issues from a scientific perspective on bioethics. The Princeton professor's new book provides insight into and ammunition against almost any anti-biotechnology argument scientists are likely to encounter.

Challenging Nature
The Clash of Science and Spirituality at the New Frontiers of Life

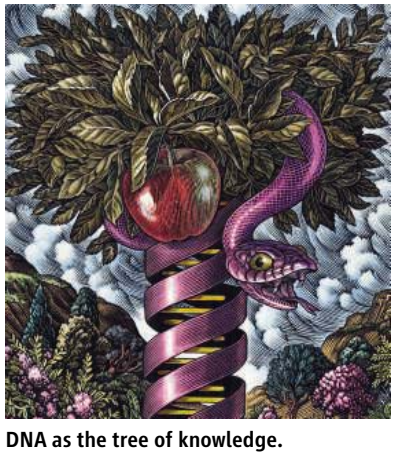
by Lee M. Silver

Ecco (HarperCollins), New York, 2006. 460 pp. $26.95, C$34.95. ISBN 0-06-058267-7.

Silver states his prejudice at the outset. His field of molecular biology, Silver claims, is, "compared with every other field of scholarship and science … the *least* compatible with spiritual beliefs." He asserts that "[b]iotechnology could alleviate human suffering, increase the quality of life in all societies, and maximize the health of the biosphere." In fact, he believes that "human nature will remake all of Mother Nature.… The ultimate question—the very asking of which strikes fear into the hearts of many people—is whether or not the human *spirit* or *soul* will stay the same or be remade in the process as well." Despite this introduction and a couple of chapters that explore the meaning of spirit, soul, and the afterlife in various cultures, in the book Silver concentrates more on broad aspects of relations between biotechnology and society than on the tension between religion and science.

Challenging Nature captures the best examples of preposterous behavior from opponents of biotechnology. Of the former chair of President Bush's bioethics council, Leon Kass, Silver quips, "Mysticism, however, does survive in some people who have enough scientific training to know better." But the author's criticism of Jeremy Rifkin is even more acerbic. "Rifkin has no academic degrees in science, technology, or agriculture, but that hasn't stopped him from writing over a dozen books supposedly aimed at explaining science to the layman while getting much of the science wrong."

Many scientists are afraid to ask what differentiates humans from all other animal species. The Christian view is still heavily influenced by the idea that the human spirit remains beyond scientific inquiry. In Silver's view, the major emphasis of human genome analyses in the Western world has been to enhance health, but some investigators (including researchers at the RIKEN Institute in Japan) have been asking how we differ genetically from chimpanzees. Silver thinks that one day the difference will boil down to a few dozen genes, a kind of "soul code." Of his host at RIKEN Silver writes, "Sakai yearns to answer a question possibly as old as humankind itself: What gives a human being a human mind with the ability to ask the question 'What gives a human being a human mind?'" These investigators were "trying to find the DNA code for the human soul." When Silver asked the researchers at RIKEN whether or not they might one day try to transfer those very genes into a nonhuman primate, their answer was affirmative: they would, if they could, try to imbue a chimp with a human soul. The Neandertal genome projects may provide even more exciting information for the next edition of Silver's book.



DNA as the tree of knowledge.

The author has a charming way of turning any argument upside down in a kind of reductio ad absurdum. Silver polls a group of scientists and bioethicists about what they would do should an infertile couple want to avail themselves of an assisted reproductive technology that had a 28% risk of birth defects. Most, in time, agreed that the parents should have that choice. Yet many people would call an 8% chance of birth defects after a hypothetical gene transfer protocol just too risky. Further reminding us that no technique is safe, Silver points out that natural fertilization—which entails a 50% risk of embryonic demise, 20% rate of fetal loss, and 4% rate of birth defects—establishes a very low bar on "safety" for reproductive technologies like cloning and germline gene alteration. Although Silver's approach fails to convince me that we should forge on with controversial reproductive technologies just because we can, it is a keen reminder that no procedure is risk free.

Silver shows himself as much at odds with mainstream ecologists and conservation biologists as he is with the religious right. Challenging the notion that ecosystems are in a fragile and optimum equilibrium, he rejects three major arguments for species preservation. In fact, he holds, there is no defensible reason for the conservation of species except because we think species preservation is a moral imperative. Although there are always some species on the edge of extinction, extinction cannot always be negative: most species that ever existed are now extinct, and that clearly hasn't been bad from our perspective. Silver criticizes the rejection of genetically modified foods on the grounds that it is based not on science but purely on an emotional feeling that natural is good and corporate is bad. As a true-to-form cheerleader for technology, he states that "The best hope for preserving and protecting wilderness and wildlife—while feeding humankind—will come not from banning biotechnology but from embracing it and guiding it."

Will *Challenging Nature* change anyone's mind about biotechnology and spirituality? Probably not. Nonetheless, it provides a good injection of the rationalist view into one of the most important debates of our time. And Silver does so in a way that should be equally accessible and enjoyable to the general reader and the professional scientist, ethicist, or theologian.

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10.1126/science.1132808

MOVIES: TRANSPORTATION

A Battery-Powered Car Run Down

David A. Kirsch

Asked in a recent interview about his "worst" business decision, General Motors (GM) chief executive officer Rick Wagoner reportedly replied: "Axing the EV1 electric car program and not putting the right resources into hybrids" (*1*). Viewers of Chris Paine's new documentary *Who Killed the Electric Car?* will not disagree.

The movie certainly makes the company look bad. The drama revolves around GM's decision to terminate leases on the thousand-odd EV1s it placed in service in California (and Arizona) during the late 1990s. The enthusiastic lessees wanted to keep using (and paying for) the cars. The most effective—and affective—scenes show 80 EV1 drivers pleading with GM to accept a $1.9 million check in exchange for the right to once again drive their electric cars. This is the language that companies should understand. When GM declines, the EV1 supporters stage an extended vigil outside the Burbank, California, storage facility housing the recalled cars. The vigil ends when local police are forced to arrest several activists so that GM can transport the vehicles from Burbank to a facility in the Arizona desert. GM spokesperson Dave Barthmuss claims that each recalled car will be donated to a museum or used for research: "We're not going to just crush it and send it off to a landfill." Circling the Arizona site in a rented helicopter, Paine's camera tells a different story. Over a somber score, crushed EV1s stand in neat piles next to the massive compactor that did the deed. It is powerful stuff, and critics of GM and the automobile industry can be forgiven for drawing sinister conclusions.

Who Killed the Electric Car?

by Chris Paine

Sony Pictures Classics, New York, 2006. 92 minutes. www.sonyclassics.com/whokilledtheelectriccar/

The short answer, therefore, to the question posed in the film's title is "the auto industry." The car companies "killed" the electric car by halting production and failing to renew leases as they expired. But the movie does not stop there. Paine wants to understand why powerful interests turned their backs on what looked like a promising market for electric cars. To its credit, the film does not hide behind the "better battery bugaboo"; ceteris paribus, available storage batteries were good enough. Other parties judged guilty, however, include the federal government, state regulators, and the oil industry. The film also faults the distant promise of the hydrogen fuel cell and consumers who—by traditional metrics—failed to show sufficient support for the fledgling electric car market.

Funeral proceedings. In July 2001, EV1 enthusiasts held a mock funeral in Los Angeles to draw attention to GM decision to pull the vehicle off the road.

Is there a mass market for electric cars? This question animates the film and public debate about the fate of the electric car. If the answer is "yes," the industry deserves the criticism it receives, and more. If not, the high-profile enthusiasts must accept that the mainstream car buyer does not share their preferences. The movie sides with the supporters of the electric car, but history suggests caution. The market for electric cars has always been small. The electric car has never been a replacement for the family sedan (*2*), and the situation today is no different. The film reports that thousands of consumers were on a waiting list to lease an EV1. But Barthmuss, the GM spokesman, responds that only about one percent of these leads ultimately resulted in leases.

The highly divergent views make for good drama, but the true size of the market for electric cars is probably somewhere in the middle. Did GM market the electric car as effectively as possible? Surely not. Nonetheless, the electric car is a niche product, and small markets mean small profits. It is silly to think, as some have suggested, that GM wanted the electric car to fail. The fate of EV1 is an indication of dysfunction in General Motors, not malevolence. Given GM's financial situation, the company cannot be faulted for exiting an unprofitable line of business.

Recent research points to the plug-in hybrid as a better path to electrifying our road transport system (*3*, *4*). After living through the events described in *Who Killed the Electric Car?* most of the film's protagonists agree. By illustrating how disruptive technologies often fail, Paine's film advances this worthy agenda while also telling a good story.

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10.1126/science.1132883

BROWSING

The American People.
Census 2000. Reynolds Farley and John Haaga, Eds. Russell Sage Foundation, New York, 2005. 470 pp. Paper, $35. ISBN 0-87154-273-0.

Beginning in 1790, the United States has conducted a national census every ten years. A short-form questionnaire sent to all households provides information about age, sex, ethnicity, household relationships, and tenure. Since 1940, additional data have been gathered with a long form sent to a sample of the population (in 2000, to one in six households). This volume distills important findings from the 2000 Census for a broad audience ranging from policy-makers to interested citizens. One section covers trends in socioeconomic progress, poverty, inequality, and employment. Another discusses patterns in marriage, families, and the welfare of children. A third explores the effects of immigration and differential population growth among racial groups. Kenneth Prewitt, former director of the Census Bureau, contributes an essay on the politics and science of census taking. The book may be the last of its kind, as future decennial censuses are to use only the short form; more detailed demographic and economic data will instead be collected on a continuous basis through the American Community Survey.

POPULATION

The Demography of Growing European Identity

Younger Europeans are more likely than older groups to consider themselves to have a European identity in addition to their national one.

Wolfgang Lutz,[1,2]* Sylvia Kritzinger,[3] Vegard Skirbekk[1]

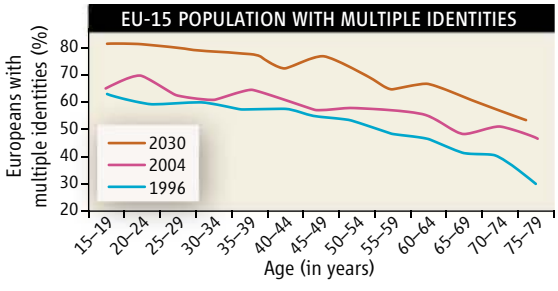
The process of European integration appears to be in disarray. After rejection of the new European constitution by referenda in France and the Netherlands and serious quarrels over the future budget of the European Union (EU), observers have warned that the EU is entering a period of stagnation or even disintegration (*1*, *2*). But observers should not be overly impressed by short-term events and need to study the important underlying forces. One such force is the slowly evolving feeling of identity in the national and European context. Here we study the trends in identity and project them into the future.

Easton (*3*) suggested that development of identity is crucial for the legitimacy of a political system. Eurobarometer (EB) surveys provide a consistent series of accessible data with individual answers to the following question: "In the near future, do you see yourself as [Nationality] only, as [Nationality] and European, as European and [Nationality] or European only?" We combined the three categories that have at least some European element, and called this category "multiple identities"(*4*).

PREVALENCE OF MULTIPLE IDENTITY

Country	Percent*
Luxembourg	78
Italy	72
France	68
Spain	64
Belgium	59
Netherlands	59
Germany	56
Denmark	54
Ireland	53
Austria	51
Portugal	50
Greece	46
Sweden	45
Finland	43
UK	40

*Average of 1996–2004



In the EB survey of 2004, 42% of the population above age 18 said that they felt themselves to be solely nationals of their own country, whereas 58% gave an answer that reflected at least some European identification. This implies that 130 million adult citizens of the EU-15 consider themselves only as nationals and 177 million as having multiple identities. But there are differences by country of residence (see table) and by age (see chart). The older the respondents, the higher is the chance that they feel only a national identity.

Do these data allow us to make projections? No, because this empirical pattern at only one point in time could be due to (i) a cohort effect, i.e., the current younger generations having been socialized in such a way that they will maintain their multiple identities throughout their lives, or (ii) an age effect, which would assume that peoples' identities change over their life course. Age profiles at different points in time (which the EB data provide) allow us to distinguish between these possibilities.

When the data for 1996 (the first year after the EU expanded to 15 member states) are compared to those for 2004, the proportion with multiple identities was lower at each age in 1996, although the general shape of the curve was maintained. This upward shift of the profile from 1996 to 2004 indicates that the pattern is not primarily due to an age effect, but rather is dominated by cohort effects. Visual analysis also shows that the curve is not merely shifted upwards, but that the humps and valleys are also shifted to the right, i.e., along cohort lines.

This visual pattern was confirmed analytically by a demographic age-period-cohort model (*5*). The model shows a strong and highly significant positive cohort effect. The coefficient we calculated of 0.48 means that for cohorts born 1 year later, the proportion with some European identity is on average half a percentage point higher. An age effect also mattered, but only to a secondary degree, with the tendency to multiple identities reaching a peak around age 50 to 60 and then starting to decline around an age that seems to coincide roughly with retirement age.

This quantification allows us to forecast future trends by assuming that the estimated effects will continue to prevail over the coming 25 years. In 2030, under the stated assumptions, there will be only 104 million adult EU-15 citizens who have strictly national identities and 226 million with multiple identities. Age-specific proportions with multiple identities in 2030 show a marked upward shift. In the age group 30 to 44, those who have some identity as Europeans will outnumber those with strictly national identities by more than three to one.

To test the sensitivity of our results to political events at the European level, we ran an alternative model that included dummy variables for 3 years, reflecting the negotiations of the Amsterdam and Nice Treaties, as well as the introduction of the Euro (*6*). This did not change the results. Multivariate models, including education, urban versus rural place of residence, and occupation, showed that those segments of the population that are likely to increase in size have more multiple identities (*6*). In addition, changing socialization processes such as expanding European-level media impact, increasing mobility of students and tourists, as well as labor migration within the EU, may also enhance the prevalence of European identity.

Our conclusion is that as older, more nationally oriented cohorts die, there are likely to be significant changes in the pattern of European identity. Although the politics of European integration remain volatile and unpredictable, these long-term tectonic shifts in identity are likely to have major and enduring consequences for the future of Europe.

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6. For detailed information and analyses, see supporting online material.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5798/425/DC1

10.1126/science.1128313

Congratulations to Lowell Thomas Medalists

Presented annually by The Explorers Club and Rolex Watch U.S.A., the 2006 honorees represent five pioneers who are making important contributions to conserving the rich biodiversity found in treetops around the world and educating the public about their importance.

M. Soubadra Devy, Ph.D.
(Fellow, Ashoka Trust for Research in Ecology and the Environment) for her pioneering work in tropical forests of India, especially pollination ecology

Francis Hallé, Ph.D.
(Botanist & Professor of Tropical Botany, Montpelier France) for his work on tree architecture and design/leadership of the "Canopy Raft"

Margaret Dalzell Lowman, Ph.D.
(Professor and Director of Environmental Initiatives, New College of Florida) for solving forest diebacks, and inspiring millions of children and students via public science outreach

Mark W. Moffett, Ph.D.
(Ecologist, writer, photographer) for his ant research, and bringing forest canopies into millions of living rooms through National Geographic magazine articles

Brian Alexander Rosborough
(Founder Chairman, Earthwatch Institute) for funding the first long-term canopy research

PHYSICS

Jump-Starting Quantum Error Correction with Entanglement

When quantum signals are sent through communication systems, they get degraded. The resulting errors can be corrected with less computational effort by taking advantage of certain quantum-mechanical effects.

Daniel Gottesman

Today's communications networks are filled with Web pages, e-mails, telephone conversations, video clips, financial transactions, and more, all encoded digitally as bursts of light flashing through fiber-optic cables. All of these messages can be boiled down to sequences of bits, 0's and 1's—usually long sequences, measured in kilobits, megabits, or sometimes even gigabits. But light, like everything else, behaves according to the laws of quantum mechanics, and a sequence of bits is not a good way to describe the properties of a quantum object. Instead, we should turn to quantum bits, or "qubits," and someday, perhaps, today's network traffic will be supplemented by streams of such quantum information. Quantum transmissions would enable cryptographic systems to detect attempted eavesdropping, and quantum computers capable of manipulating quantum information could solve some problems far more rapidly than any conceivable classical computer. Just as classical information is encoded today in error-correcting codes to protect it against errors in transmission, quantum information will need to be encoded in quantum error-correcting codes in order to reliably reach its destination. Indeed, quantum information is more sensitive to errors than is classical information, so error correction will be even more important. On page 436 of this issue, Brun *et al.* (*1*) show how it is possible to improve the performance of quantum error-correcting codes, using a quantum state previously shared between the sender and receiver.

There are three critical properties that determine the quality of an error-correcting code, quantum or classical. Two are fairly obvious: the rate at which the code can be used to transmit data, and the error rate it can tolerate. There is, in general, a trade-off between the two—the more noise in a communications line, the slower the information gets through. For classical information, the optimal trade-off is given by the Shannon capacity of the channel (*2*). Indeed, an error-correcting code chosen completely at random will, with only a little modification, achieve the optimum channel capacity. There is a catch, however: The receiver must be able to determine what sort of error occurred during transmission in order to be able to correct it and for a random code this is an extremely difficult task. This brings us to the third critical property, the decoding time, which is usually dominated by the time required to figure out what the error is. There is a vast literature on classical error-correcting codes, and today's best codes, such as low-density parity check (LDPC) codes (*3*, *4*), come close to the Shannon bound for data rate versus error rate, yet still can be rapidly decoded.

Owing to some of the peculiar properties of quantum information, we do not yet have a good analog of Shannon's theorem for quantum transmissions, but we do have some idea of what rates are possible. Just as with classical information, a randomly chosen quantum error-correcting code gives a very good data rate and error rate. (It is not, however, always optimal, which makes it difficult to construct a quantum Shannon theorem.) But a random code will take a very long time to decode, leaving us with the problem of finding a quantum code that is simultaneously good for all three properties.

Classical error-correcting codes work by answering a series of questions, gradually accumulating enough information to identify what went wrong with the transmission. Different codes correspond to different sequences of questions. We can do something analogous for quantum error-correcting codes, and can even convert many classical codes directly to quantum codes (with a single qubit corresponding to a pair of classical bits) (*5*). Unfortunately, not all classical codes can be used in this way. Quantum mechanically, the questions that reveal the error correspond to measurements, and some pairs of quantum measurements are incompatible and cannot be

Entangled messaging. Alice wishes to send a quantum state to Bob. At some point in the past, Alice and Bob create a shared entangled state. Alice encodes her data, combining the quantum state she wishes to send with her part of the entangled state and some extra qubits. Alice sends the encoded state through a communications channel, where it undergoes some noise. Bob is now able to perform a decoding operation correcting the error and extracting the original state and a new entangled state. Alice and Bob can now send a new quantum state without having to prepare a new entangled state first.

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performed on a single state. Only if all the questions used in a code are compatible with each other can the classical code be converted into a quantum code. Because of this constraint, attempts to date to make good LDPC-based quantum codes have failed.

Brun *et al.* show that the compatibility requirement can be circumvented if the sender and receiver share a particular type of quantum state (called an "entangled state") before transmission (see the figure). Entanglement is a purely quantum-mechanical phenomenon allowing, among other things, stronger correlations between a pair of distant quantum systems than would be possible were they purely classical. The prior connection between sender and receiver allows them to cancel any incompatibility in the encoding with an equal incompatibility in the decoding (a case where two wrongs do make a right), meaning that many more classical error-correcting codes, including some of the most efficient, can be converted to quantum codes. The original entangled state must be free of noise, but a successful transmission regenerates it, allowing further communication at no additional cost in entanglement.

This result is a great boon for a sender and receiver who wish to communicate on a regular basis, because they can generate entanglement once and then use it repeatedly for efficient quantum transmissions. It is less useful for a one-time connection or for storage of quantum information over time, but even there, a less efficient code could be used to generate the first collection of entanglement, followed by multiple iterations of the scheme of Brun *et al.* LDPC codes have also attracted interest as candidates to improve fault-tolerant quantum computation, but further work will be necessary to see if the ideas of Brun *et al.* can deliver the desired advances.

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10.1126/science.1133797

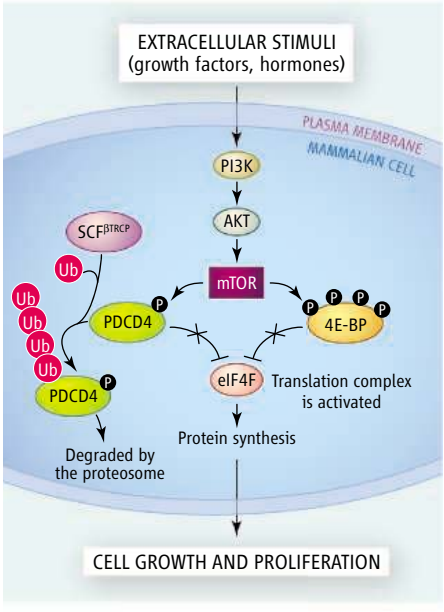
SIGNAL TRANSDUCTION

Protein Synthesis and Oncogenesis Meet Again

A protein degradation process targets a factor that blocks protein synthesis and inhibits tumor growth. Enhanced degradation of this protein may provide a growth advantage to cancer cells.

Nahum Sonenberg and Arnim Pause

The production of proteins is a prerequisite for cells to grow and proliferate (*1*). In response to mitogens, growth factors, and hormones, protein synthesis from messenger RNAs (mRNAs), frequently referred to as translation, is boosted. Many cellular signaling pathways that regulate translation factors have been elucidated. The most prominent pathway is one comprising phosphoinositide 3-kinase (PI3K) and two serine-threonine protein kinases, AKT and mammalian target of rapamycin (mTOR). The mTOR pathway transduces extracellular growth signals to the cell's translation machinery by the addition of phosphate molecules (*2*). Such phosphorylation directly controls the activity of the targets, including factors that initiate the translation process. On page 467 of this issue, Dorrello *et al.* (*3*) reveal a new signaling branch of the mTOR pathway that controls translation: the degradation of PDCD4 (programmed cell death protein 4). Not only is this factor phosphorylated by the mTOR pathway, but the modification marks it for destruction (see the figure). PDCD4 normally blocks translation and suppresses cell growth. Consequently, loss of PDC4 function is expected to result in a growth advantage to cells and ultimately lead to cancer.



Targeting protein synthesis. The eIF4F complex binds mRNA and promotes translation initiation in response to extracellular stimuli. The PI3K-AKT-mTOR signaling pathway targets two major translation inhibitors, PDCD4 and 4E-BP, for phosphorylation. This modification blocks their actions and allows protein synthesis to occur. This ultimately supports cell growth and proliferation. Phosphorylation of PDCD4 marks it for degradation. Ub, ubiquitin.

Control of translation occurs primarily at the initiation step, in which the 40*S* ribosomal subunit is recruited to mRNA and positioned at the initiation codon, the nucleotide sequence that specifies the first amino acid of the protein (*4*). The most general mechanism of translation initiation depends on the mRNA 5′ cap structure (m^7GpppN, where N is any nucleotide). The cap structure, present on all mRNAs synthesized in the cell's nucleus, is bound in the cytoplasm by a cap-binding protein complex called eIF4F (eukaryotic initiation factor 4F). eIF4F is composed of three subunits: eIF4E, the cap-binding subunit; eIF4A, an RNA helicase that unwinds the mRNA 5′ secondary structure; and eIF4G, a scaffolding protein that binds to other initiation factors.

Recognition of mRNA by eIF4F is a major target for translation regulation, and one of the best-studied mechanisms is the control of eIF4F assembly by a family of repressor proteins called 4E-BPs (4E-binding proteins). These proteins compete with eIF4G for binding to eIF4E and consequently inhibit cap-dependent translation (*5*). Importantly, the interaction of 4E-BPs with eIF4E is reduced as a consequence of phosphorylation on several serine and threonine residues of 4E-BP. The mTOR signaling pathway is the major contributor to 4E-BP phosphorylation (*6*). Thus, an important mechanism by which the mTOR

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pathway modulates cell growth and proliferation is through the control of translation initiation. mTOR phosphorylates directly several substrates, including 4E-BPs and S6 kinase. In turn, S6 kinase phosphorylates several substrates, including the ribosomal protein S6, SKAR, and eIF4B (*6*–*8*). Dorrello *et al.* identify PDCD4 as a new substrate for S6 kinase.

PDCD4 inhibits the RNA helicase activity of eIF4A, as well as its incorporation into the eIF4F complex (*9*). PDCD4 is overexpressed in cell cycle–arrested cells, and its expression is reduced in cancer cells. Reexpression of PDCD4 in cancer cells induces apoptosis and inhibits tumor growth. Dorrello *et al*. report that PDCD4 is rapidly degraded upon phosphorylation by S6 kinase, in response to activation of the mTOR pathway by growth factors. Degradation of PDCD4 is mediated by the E3 ubiquitin ligase complex $SCF^{\beta TRCP}$ (SKP1–CUL1–F-box), which tags its substrates with ubiquitin molecules for degradation by the cell's proteosome. In the absence of growth factors, PDCD4 remains phosphorylated, resulting in the inhibition of eIF4A, protein synthesis, and cell growth. Phosphorylated PDCD4 binds to $SCF^{\beta TRCP}$, becomes ubiquitinated, and is subsequently degraded by the proteosome. Thus, elimination of PDCD4 frees eIF4A to be incorporated into eIF4F for stimulation of cap-dependent translation initiation. It is intriguing that the mRNA-binding complex eIF4F is the target of two different translation inhibitors, 4E-BP and PDCD4, both of which are regulated by the mTOR pathway. The mTOR pathway has been strongly implicated in the etiology of many human cancers, thus linking cell growth, translation, and oncogenesis.

Dorrello *et al*. were searching for substrates for $SCF^{\beta TRCP}$, a multisubunit complex that contains an E2 ubiquitin-conjugating enzyme and substrate recognition subunits called F-box proteins (of which there are 68) (*10*). One of the F-box proteins is βTRCP. $SCF^{\beta TRCP}$ is constitutively active in the cell and selects substrates based on their phosphorylation, which enables binding to βTRCP. Dorrello *et al*. discovered new substrates for $SCF^{\beta TRCP}$ by using mass spectrometry to identify associated, ubiquitinated proteins. This method is very efficient because substrates of E3 ligases are of low abundance in the cell.

The study by Dorrello *et al*. represents the second example of control of translation initiation by the ubiquitin system. Recently, Yoshida *et al*. showed that the amount of Paip2, a translational repressor, is controlled by binding to the E3 ligase EDD (*11*). Paip2 binds to poly(A)-binding protein (PABP), a eukaryotic protein that binds to the 3′ poly(A) tail on mRNA to control translation. Interestingly, the binding of Paip2 to EDD is determined by the amounts of PABP in the cell, because PABP shares a common sequence with EDD. It will not be surprising if we find that translational control through ubiquitination is a widespread mechanism to regulate translation and, ultimately, cell growth.

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10.1126/science.1134031

ASTRONOMY

Cosmic Rays Track the Rotation of the Milky Way

Energetic cosmic rays are coming from a particular region of the sky and rotating with our arm of the Milky Way. Such data may help us understand how our Galaxy interacts with the Sun's magnetic field.

Marc Duldig

Cosmic rays are extremely high-energy nuclei that travel close to the speed of light. They are ubiquitous in the Milky Way and make up a substantial fraction of the total energy of the Galaxy, equivalent to the energy in large-scale magnetic fields and thermal gases. Their composition largely reflects the natural abundance of the elements in the Galaxy, mostly protons (hydrogen nuclei), some alpha particles (helium), and a tiny fraction of the heavier elements. Being charged particles, they are deflected when crossing magnetic fields, but the amount of deflection is dependent on their momentum. The cosmic-ray flux at energies high enough to undergo minimal deflection is so small that sources have proved impossible to observe directly. On page 439 of this issue, however, Amenomori *et al.* (*1*) report the direct observation of an excess signal in cosmic rays coming from the Cygnus region of the sky using a detector array in Tibet. This excess could be either cosmic rays of very high energy or high-energy gamma rays that would likely be associated with cosmic-ray sources. Furthermore, they have also shown that the cosmic-ray gas at these very high energies is rotating with the local spiral arm of the Galaxy, confirming behavior previously only seen at lower energies with cosmic rays influenced by the Sun's extended magnetic field.

The difficulty in achieving such observations can be most readily understood when we look at the full cosmic-ray spectrum, as shown in the figure. The spectrum is approximately a power law, but there are features within it that mark probable changes in the sources. Below about 10^{15} eV, they are almost certainly produced in the shocks from supernovae, but at higher energies there is a steepening in spectrum and a change in the relative elemental abundances, indicating changing source mechanisms. There are further changes in composition at the "ankle," and the origin of particles at the highest energies observed is problematic.

At the lowest energies, the cosmic rays are plentiful but are heavily influenced by the solar magnetic field, which is carried beyond the planetary orbits [100 astronomical units (AU) or more, where 1 AU is the mean Earth-Sun distance, or about 1.5×10^8 km] by the gusty plasma wind that emerges from the Sun (the solar wind). This field is complex and dynamic, with shocks propagating from active regions on the Sun and an outer bound-

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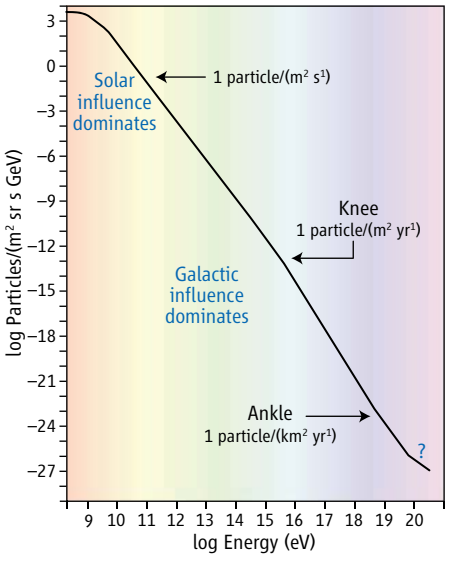

Cosmic-ray spectrum. Distribution of cosmic-ray flux as a function of particle energy. At low energies, solar magnetic fields strongly influence cosmic-ray propagation. At high energy, the minimally deflected cosmic rays that would reveal source location are far less intense and thus much harder to detect.

ary shock that defines the region known as the heliosphere. Low-energy cosmic rays entering the heliosphere lose any information about their arrival direction in reaching the inner solar system as a result of substantial deflections and scatterings.

The motion of cosmic rays in a magnetic field is described by a transport equation that takes into account the convection, diffusion, drift, and adiabatic energy loss (if the field is converging) or gain (if the field diverges). This equation was first described by Parker (*2*, *3*) and, in the case of the heliosphere, further developed by others such as Forman and Gleeson (*4*). The equation predicts that the lower-energy cosmic-ray gas should move with the Sun's magnetic field, which rotates with the Sun with a 27-day period. Such behavior is called corotation. Corotation has been observed for many years in lower-energy observations ($<5 \times 10^{10}$ eV) and causes the largest long-term anisotropy observed in this energy range [see, for example, Hall *et al*. (*5*) and references therein]. Above about 10^{11} eV, solar influence declines, and the magnetic field of the local spiral arm of the Galaxy is expected to be the controlling feature for cosmic-ray propagation. However, the flux of comic rays is reduced by 10 orders of magnitude from the low-energy part of the spectrum, and thus very large detection areas and equipment operation with long-term stability are needed to achieve the necessary statistics to search for directional enhancements that are only fractions of a percent.

Amenomori *et al*. have found directional enhancements in the 10^{12} to 10^{15} eV energy range and have also shown that the cosmic rays are corotating with the local spiral arm of the Galaxy. This requires the local spiral-arm field extent and strength to be sufficient to trap the cosmic-ray gas rather than to allow it to flow past the heliosphere and generate an anisotropy caused by the relative motion of the heliosphere and the gas—the so-called Compton-Getting effect. This anisotropy is just like walking in still air—the wind is felt from the direction in which you walk because of your relative motion. Amenomori *et al*. see the effect due to motion of Earth in its orbit, giving confidence in their results, but when this effect is removed there is no residual effect that would indicate residual motion between the heliosphere and the cosmic-ray gas. This gives additional constraints to models of the local spiral arm and the field within it.

The next step in the research is to deduce the nature of enhancements that they have found. The researchers must differentiate between cosmic-ray particles or gamma rays as the source. The Tibet air shower experiment observes the particles of an atmospheric cascade produced by cosmic rays. This cascade involves the production of very high-energy gamma rays that then undergo pair production with the positrons annihilating and producing further gamma rays. If the initiating interaction is a gamma ray and not a particle, it is not a trivial exercise to differentiate the responses, but it can be and has been done by other groups. The Tibet air shower team will now enhance their system to achieve this differentiation, and we can look forward to further results from the experiment. Of course, increased statistics with time will also allow the group to dig deeper into the signal and possibly find more subtle anisotropies and to more clearly define the enhancements they have found. It will also be extremely interesting to see what, if any, differences in the lower-energy anisotropies they observe following the next solar magnetic reversal in a few years. This could tell us a great deal about how the heliosphere and the local spiral-arm field interact.

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10.1126/science.1134046

CHEMISTRY

The Future of Organic Synthesis

Peter Kündig

A variety of new synthetic methods, together with increased automation, are revolutionizing the synthesis of complex molecules such as found in natural products.

The extreme structural diversity found in many natural products poses an extraordinary challenge to chemists trying to synthesize these molecules (*1*). Many natural products are available only in trace quantities from natural sources, making total or partial synthesis a necessity. For example, the drug Taxol, an anticancer natural product, is present only in minute quantities in the bark of *Taxus brevifolia*. A closely related compound, 10-deacetylbaccatin III, can be extracted from leaf clippings from *Taxus baccata* with no harm to the tree (*2*). During studies of the transformation of 10-deacetylbaccatin into Taxol, a compound was synthesized that turned out to be more soluble and twice as active as Taxol itself (*3*). This compound was developed into the drug Taxotere. Total and partial syntheses of bioactive natural products and derivatives also provide the driving force for the invention of new reactions with ever-increasing levels of efficiency and selectivity.

Frontier synthesis and catalysis figured prominently at the first chemistry symposium organized by all national European chemical societies (*4*). The presentations focused both on new synthetic and catalytic procedures and on new ways to do synthesis. This Perspective highlights key advances in both areas.

The synthesis of complex molecules requires patience, stamina, and a profound

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knowledge of reaction mechanisms. Even for moderately complex molecules, it is not uncommon to require at least 10 steps and sometimes many more. Side reactions produce waste, reduce efficiency, and result in a sharp drop of available material after only a few synthetic steps. Tuning of reactions, work-up, and purifications are all extremely time-consuming. Such syntheses bring to light the limitations of current chemical transformations. The drive for shorter and more efficient synthesis procedures will continue to challenge the resourcefulness of synthetic chemists.

Flow technology. The seven-step sequence of (±)-oxomaritidine synthesis has been carried out in a fully automated flow reactor (*18*).

Chemists have developed numerous methods to address these challenges and facilitate natural product syntheses. Major advances in catalytic applications have been made. Stable, readily synthesized ruthenium and molybdenum catalysts that allow the exchange of substituents between different olefins (metathesis; 2005 Nobel Prize in chemistry to Y. Chauvin, R. H. Grubbs, and R. R. Schrock) are now routinely used in organic synthesis. Chiral amines have been rediscovered as catalysts, and very elegant, asymmetric, and useful synthetic methods have emerged (*5*). New, more efficient variants of classical metal-catalyzed carbon-carbon coupling reactions allow alkyl coupling and aryl chloride coupling reactions under mild conditions (*6*). Bifunctional catalysis (*7*, *8*) and tandem and multistep catalytic processes all convert very simple small molecules in a series of reactions into highly functionalized complex molecules; these processes have become prominent (*9*). Directed evolution of enzymes for synthesis and the combination of metal-catalyzed reactions with enzymes are also very promising developments (*10*, *11*).

Combinatorial approaches and high-throughput experimentation are also firmly established. They are complemented by the synthesis of self-adaptive combinatorial libraries (*12*).

The need for cleaner, more sustainable chemical practices also poses new challenges. Environmentally benign chemistry and sustainable processes require new ways of carrying out synthesis (*13*). Hence, in addition to the development of new reactions, reagents, and catalysts, novel ways to assemble molecules are an important driver for organic synthesis.

Automated synthesis, in which robots and machines carry out much of the tedious bench work, has made its entry into research laboratories (*14*). The substitution of conventional work-up, isolation of products, and separation of catalysts and reagents by new techniques is of major importance. Very promising steps in this direction are now in hand. For example, Leitner and co-workers reported a catalyst cartridge system based on a rhodium complex immobilized on a polymer backbone, combined with supercritical CO_2 as solvent and separation system. This allowed a series of catalytic reactions to be carried out sequentially (*15*). Related work has also been reported by Webb and Cole-Hamilton (*16*).

To facilitate the multistep synthesis of complex molecules, Ley and co-workers have turned to the use of solid-supported reagents in a designed sequential and multistep fashion without the use of conventional work-up procedures. They extended these concepts to make use of advanced scavenging agents and catch-and-release techniques, and combined them with continuous-flow processing to create even greater opportunities for organic synthesis.

Using these flow chemistry methods, the group recently completed the syntheses of the natural products grossamide (*17*) and oxomaritidine (*18*) (see the figure). The automated sequence that produces racemic oxomaritidine from readily available starting materials in less than a day is the first multistep flow-through preparation of a natural product. As such, this represents a milestone in method development.

The syntheses required the construction of a fully automated continuous-flow reactor system, with immobilized reagents packed in columns to effect the synthesis steps efficiently. Once set up, the new techniques allow the rapid and scalable automated syntheses of sophisticated molecules. The tools used (including a Syrris AFRICA system, a microfluidic reaction chip, and a Thales H-Cube flow hydrogenator) are still far from being household names to synthetic chemists, but this may change very soon. This emerging field could well cause a paradigm shift in the way chemical synthesis is conducted.

Will such automated syntheses put synthetic organic research chemists out of jobs? Hardly, but it will provide them with more time to dream up and develop new and improved transformations and catalysts.

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10.1126/science.1134084

CHEMISTRY

Toward Molecular Imaging with Xenon MRI

Biosensors that include xenon as the signal source dramatically increase the sensitivity of magnetic resonance imaging and may have extensive clinical application.

Bastiaan Driehuys

When it comes to molecular imaging—the burgeoning discipline of visualizing biological processes at the cellular and molecular level in living organisms—magnetic resonance imaging (MRI) is low on the list of favored techniques (*1*). The receptors and gene expression products that we aim to observe by molecular imaging are present at minuscule concentrations (around 10^{-6} to 10^{-12} mole per liter) in the body. Yet the nuclear magnetic moments that provide the signal in MRI are tiny, and lots of them are needed to generate an image. MRI is thus limited to detecting concentrations of 10^{-3} to 10^{-5} mole per liter. In contrast, radioisotope imaging methods such as positron emission tomography and single photon emission tomography can detect probe molecule concentrations of 10^{-9} to 10^{-12} mole per liter. These techniques have been the natural choice for molecular imaging, although they lack the spatial and temporal resolution of MRI and make use of ionizing radiation.

Enhanced online at www.sciencemag.org/cgi/content/full/314/5798/432

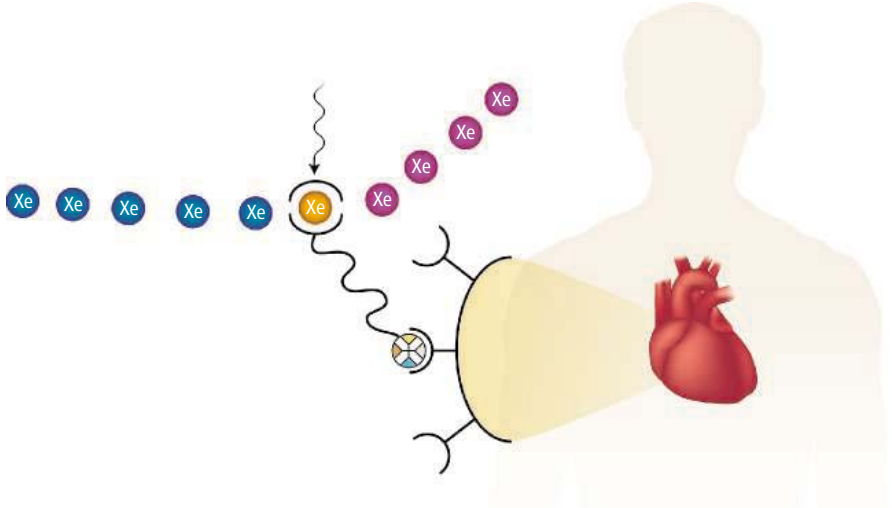
On page 446 of this issue, Schröder *et al.* (*2*) report an important step toward changing this conventional wisdom by introducing a new technique, dubbed HYPERCEST, that could make MRI competitive in the molecular imaging game. By combining elements of atomic physics, synthetic chemistry, and magnetic resonance trickery, the authors create the compelling vision of a comprehensive MRI examination that provides diagnostic information at the molecular, functional, and anatomic levels.

To increase the sensitivity of MRI, the authors use hyperpolarized ^{129}Xe gas, so named because the nuclear alignment (polarization) of the ^{129}Xe atoms is five orders of magnitude higher than that achieved by the MRI magnet (*3*). The resulting 100,000-fold signal enhancement makes it possible to image the inhaled ^{129}Xe gas in the lungs with exquisite resolution, even though it is less dense than water (the usual MRI signal source) by a factor of 3000.

When hyperpolarized ^{129}Xe is inhaled into the lungs (or injected in a carrier fluid), it dissolves in the blood and is circulated throughout the body, where it could be imaged in all tissues. However, although the signal enhancement achieved through the use of ^{129}Xe is an impressive start, it is not sufficient to enable molecular imaging. Further sensitivity enhancement is needed, and a means is required to obtain specificity to particular molecular targets of interest. To address these remaining issues, Schröder *et al.* turned to xenon biosensors.

Xenon biosensors are supramolecular constructs consisting of a cage, a linker, and a targeting moiety such as an antibody or ligand that causes the sensor to bind to a specific biological target in the body (see the first figure). This specific molecular binding lets the sensors accumulate in the type of pathology they were designed to find, such as tumors or atherosclerotic plaques. Ironically, the way to detect the presence of such bound sensors is by using them to extinguish the hard-won signal from the hyperpolarized ^{129}Xe gas. An enormous sensitivity gain arises from the fact that one biosensor can snuff out the signal from potentially thousands of nearby ^{129}Xe atoms.

^{129}Xe atoms are continually diffusing in and out of the cage of the biosensor. During their millisecond-long stay in the cage, the ^{129}Xe atoms experience a unique shift in their resonance frequency, which makes them readily identifiable. Continuous application of radio-frequency radiation at this frequency causes the signal from any ^{129}Xe atom that enters the cage to be erased. Because irradiation can take place for many seconds, thousands of ^{129}Xe atoms can be affected. By imaging the distribution of ^{129}Xe after irradiation, the presence of accumulated biosensors (and thus pathology) is manifested as a dark region in the ^{129}Xe image.



The future of MRI. Xenon biosensors may provide a means to use magnetic resonance imaging to visualize molecular binding events in the body at minute concentrations.

The vision, then, is this. A patient, who is predisposed to heart troubles, comes to the hospital and is injected a few hours before imaging with a low concentration of biosensors designed to bind to a marker associated with atherosclerosis. The biosensor may, for example, bind to matrix metalloproteinases, which are elevated in plaques that are vulnerable to rupture (*4*). The patient is then placed in the MRI scanner and inhales a lungful of hyperpolarized ^{129}Xe, which distributes throughout his body. While it distributes, the ^{129}Xe is irradiated at its unique biosensor-bound frequency. Subsequently, the remaining ^{129}Xe distribution is imaged, and regions where biosensors have accumulated in vulner-

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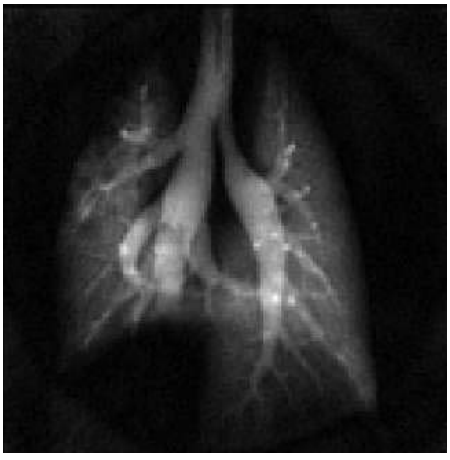
able plaque appear as dark spots. In the same exam, a high-quality image of blood flow through the coronary arteries and anatomical landmarks of the heart can be made using conventional MRI techniques. On the basis of this comprehensive study, the physician can prescribe a treatment plan that is tailored to the individual patient. Moreover, such noninvasive imaging procedures, once validated, could be used to quickly test the efficacy of novel therapeutic compounds in much smaller numbers of patients than required in current clinical trials.

Schröder *et al*. report a promising path toward nanomolar-sensitivity molecular imaging. However, imaging ^{129}Xe in tissues beyond the airspaces of the lung is in its infancy. As ^{129}Xe moves from lung to blood and tissues, its concentration is reduced by a factor of 10 or more, making imaged correspondingly more challenging. Recently, the lungs of living rats were imaged to reveal the ^{129}Xe distribution at the micrometer scale in the airspaces (see the second figure) and at the millimeter scale in the pulmonary blood and tissues (*5*).



Imaging with xenon. This ^{129}Xe MRI image shows the lungs of a rat at a resolution of 300 μm (*5*).

Progress from imaging ^{129}Xe in the tissues of rats to imaging ^{129}Xe in the tissues of humans will require larger volumes of hyperpolarized ^{129}Xe to be produced and delivered. Ruset *et al.* recently reported a ^{129}Xe polarizer prototype that produces several liters of ^{129}Xe in 10 min (*6*). Such production, once routine, would be more than enough to meet this challenge.

Finally, biosensor formulations for specific molecular targets must be developed, and their biodistribution and safety validated. Much remains to be done, but it is not every day that a favorite imaging technique gains three orders of magnitude in sensitivity.

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10.1126/science/1134532

SIGNAL TRANSDUCTION

Prelude to an Anniversary for the *RAS* Oncogene

A recent conference focused on the role of *RAS* in cancer, nearly a quarter of a century after its identification as the first human oncogene.

Julian Downward

In 1981, groups led by Robert Weinberg, Michael Wigler, and Geoffrey Cooper discovered that small fragments of DNA taken from human cancer-derived cells could endow malignant characteristics on normal mouse fibroblast cells. Within a year, the same groups, along with that of Mariano Barbacid, established that the active ingredient in transforming DNA from a human bladder cancer cell line was the cellular homolog of H-*RAS*, an oncogene found in the Harvey rat sarcoma retrovirus. They thus demonstrated for the first time that human tumors contained activated oncogenes, related to those picked up by retroviruses from their host genomes. Within a few months, the same groups further found that the difference between the normal human H-*RAS* gene and the oncogenic form found in tumors was a single point mutation. It soon became clear that a very high proportion of human tumors contain such activating mutations in *RAS* oncogenes (*1*). Thus began the burgeoning area of research into the three closely related proteins, H-, K-, and N-RAS, henceforth collectively referred to as RAS. The imminent quarter-century anniversary of the identification of the first human oncogene was marked by a recent conference in Glasgow (*2*).

With so much work on RAS behind us, what has been achieved and where are we heading? The realization that mutations in *RAS* oncogenes play a causal role in more than a quarter of human cancers has kept RAS and the signaling pathways it controls firmly in focus as therapeutic targets (*3*). They are small GTP-binding proteins that, when acted upon by specific factors, cycle between an activated and inactivated form—RAS-GTP and RAS-GDP, respectively. RAS proteins are tethered to the inner cell membrane, coupling growth factor receptors to downstream signaling pathways that control cell growth, proliferation, survival, and transformation (see the figure).

Blocking the activity of RAS by means of farnesyltransferase inhibitors, which prevents membrane localization, has proved disappointing in the clinic. Other ways of targeting RAS itself have not been developed. However, there is currently much excitement surrounding drugs that inhibit downstream signaling cascades controlled by RAS. These include the RAF–mitogen-activated protein kinase kinase (MEK) pathway and the phosphatidylinositol 3-kinase (PI3K)–AKT pathway, both of which control cell growth. In addition to RAS, two direct effectors, the B-RAF isoform and PI3K (specifically, the p110α subunit), are frequently activated by point mutation in human cancers (*4*). Potent inhibitors of MEK, the direct target of RAF, are showing promise in clinical trials, although it is not clear that B-RAF or RAS mutational status correlates with outcome.

"Oncogene addiction," the notion that tumor cells become reliant on the continued function of activated oncogenes, is an attractive hypothesis for drug developers but clearly does not always hold true. During the complex evolution of a tumor, the total set of acquired mutations will no doubt affect the degree of continued dependence on early oncogenic events such as RAS activation. Other drugs targeting the RAF-MEK path-

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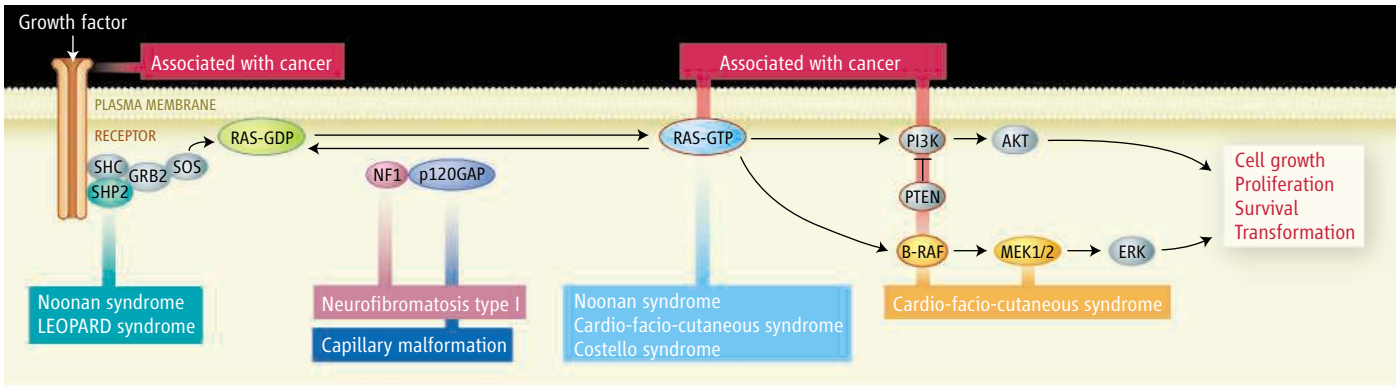

Mutations in RAS signaling pathways are associated with human disorders. Components marked in red undergo frequent somatic mutation in cancer. Other components undergo germline mutation in developmental disorders, as indicated, some of which are characterized by cancer predisposition.

way include sorafenib, designed as a RAF inhibitor, which has been licensed for treatment of renal cell carcinoma, although its effectiveness depends on its broad specificity, including against angiogenic growth factor receptors. It has not shown activity as a single agent against human melanomas, where B-RAF activation rates are very high.

The therapeutic value of inhibiting the RAS-PI3K-AKT signaling pathway in tumors bearing activating mutations in p110α or RAS, or deletions of the tumor suppressor gene PTEN (which encodes a phosphatase that reverses the action of PI3K), is still uncertain. However, at least six companies have drugs that inhibit PI3K in late preclinical development, so this question should be answered in the next few years.

A surprising recent development in our understanding of RAS function has been the discovery that germline activating mutations can occur in genes encoding RAS proteins and other components in these signaling pathways, resulting in developmental defects (see the figure). Costello syndrome, characterized by multiple congenital anomalies, mental retardation, and predisposition to tumors, can result from germline mutational activation of H-*RAS* (*5*). It is unexpected that continual expression of fully activated H-RAS is relatively well tolerated, underlining the fact that many other molecular steps are needed for progression to tumor formation. Noonan syndrome, characterized by short stature, facial dysmorphism, and cardiac defects, with some predisposition to tumors, can result from germline mutation of K-*RAS*, although in this case the mutations are more weakly activating (*6*). In addition, cardio-facio-cutaneous syndrome, involving craniofacial and cardiac defects but no cancer predisposition, has recently been shown to involve mutations in the genes encoding K-RAS, B-RAF, and two isoforms of MEK (MEK1/2) (*7*, *8*). It is still unclear what the effect of all these mutations is on the activity of these proteins, but some of them are at least weakly activating. On the other side of the RAS regulatory balance, germline mutations have long been known to occur in negative regulators of RAS, such as neurofibromin (NF1), resulting in type I neurofibromatosis (which includes cancer predisposition), and p120GAP, resulting in capillary malformation, a hyperplastic disorder.

An aspect of the cell biology of RAS function that has generated much interest in the past few years is that of RAS signaling from specialized areas of the plasma membrane called lipid rafts, as well as from intercellular membranes such as the Golgi apparatus, endoplasmic reticulum, and mitochondrion. RAS is directed to membrane compartments—predominantly the plasma membrane—by posttranslational modifications, including palmitoylation and farnesylation. Recent developments in the study of plasma membrane RAS signaling platforms, using electron microscopy, fluorescent imaging techniques, and computational modeling, show that different RAS isoforms are recruited to distinct "nanoclusters" that contain downstream signaling proteins such as RAF and MEK. These clusters are dynamic and small (about 10 nm in diameter), containing fewer than 10 proteins, in contrast to previous notions of lipid rafts as large and stable (*9*). Meanwhile, the issue of RAS signaling on intracellular membranes has become more complex, with evidence that RAS signaling can be activated at the Golgi apparatus and the endoplasmic reticulum. RAS can thus transmit signals from these locations and others, including mitochondria and endosomes. However, most of these observations are based on artificially overexpressed RAS proteins or domains of downstream effectors in cultured cells, often as fusion proteins with fluorescent markers. There remain concerns that the reported activation of RAS on intracellular membranes by upstream regulators may depend on the exact nature of the fluorescent probes used to visualize them (*10*) and also that biological signals emanating from RAS at the Golgi are dispensable for regulation of proliferation and transformation (*11*). There is some way to go before the importance of RAS signaling from intracellular sites is unequivocally established, but this clearly will be an area of considerable interest in coming years.

So, nearly 25 years and some 30,000 publications on, RAS continues to provide surprises, not only from a role in oncogenesis, but also in development and as a paradigm for large swaths of molecular cell biology, including GTP-binding proteins, lipid-directed posttranslational modification, membrane trafficking, and growth regulatory signaling. It should take much less than a further quarter century to find out whether RAS has yet more important secrets to reveal, and whether its promise as an effective therapeutic target in cancer can be delivered.

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Exposure to Scientific Theories Affects Women's Math Performance

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On 14 January 2005, Lawrence Summers, then president of Harvard University, speculated that one reason why women are underrepresented in science and engineering professions is because of a "different availability of aptitude at the high end" (*1*). These remarks were met with much outcry by some critics of President Summers, and social scientists were divided in their reaction to his comments. The question of sex differences in math in the context of the nature-versus-nurture debate is not new and remains contentious. For this paper, we did not explore whether such innate sex differences exist. Instead, we investigated how women's math performance is affected by whether they are considering genetic or experiential accounts for the stereotype of women's underachievement in math. Such a question is relevant to how people respond to scientific arguments and science education more generally.

Stereotype threat is a phenomenon in which the activation of a self-relevant stereotype leads people to show stereotype-consistent behavior, thereby perpetuating the stereotypes (*2*). For example, African Americans perform worse on intelligence tests when their race is highlighted (*2*), and women's math performances decrease when their gender is made salient (*3*). Stereotype threat can be reduced when people focus on the malleability of the traits at hand (*4*).

Past research reveals that people respond differently to genetic and experiential accounts of behaviors. Undesirable behaviors with experiential causes are seen as more voluntary and blameworthy than behaviors with genetic causes (*5*). Experiential causes, in contrast to genetic ones, appear to be viewed as less impactful and more controllable. We reasoned that stereotypes about one's groups are often perceived as inescapable, because many stereotypes are viewed in essentialized terms (*6*). That is, people may view the origin of some stereotypes as resting on the perceived genetic basis that distinguishes these groups. If individuals share the same genetic foundation at the base of the stereotype, they might feel that the stereotype applies to them and hence are vulnerable to stereotype threat. In contrast, we propose that people might react differently if the origins of the group differences were perceived to rest on the specific experiences that people's groups have had. People may reason that their own experiences are different or that they can resist the effects of their experiences.

Our studies manipulated participants' beliefs regarding the source of gender differences in math and measured their subsequent math performance (Fig. 1). In study 1 (*7*), women undertook a Graduate Record Exam–like test in which they completed two math sections separated by a verbal section. The verbal section contained the manipulation in the form of reading comprehension essays. Each test condition used a different essay. Two of the essays argued that math-related sex differences were due to either genetic (G) or experiential causes (E). Both essays claimed that there are sex differences in math performance of the same magnitude. Two additional essays served as a traditional test of stereotype threat. One essay, designed to eliminate underperformance, argued that there are no math-related gender differences (ND). The other essay, designed as a standard stereotype-threat manipulation (S), primed sex without addressing the math stereotype. Controlling for performance on the first math section, we used analyses of covariance to demonstrate that women in the G and the S conditions exhibited similar performances on the second math test ($F < 1$). Women in the E and the ND conditions, although not different from each other ($F < 1$), significantly outperformed women in G and S conditions (all P values ≤ 0.01).

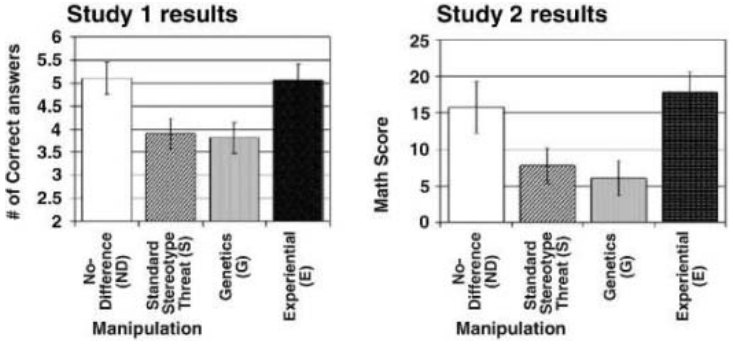

Fig. 1. (**Left**) Study 1 results. Scores on second math test (controlling for scores on first test) after reading essays. (**Right**) Study 2 results. Scores on math test after hearing manipulation.

These findings were replicated in a second study (*7*) that used a different experimental design. An analysis of variance identified significant performance differences between the conditions [$F(3,88) = 4.15$, $P < 0.01$]. Fisher probable least-squares difference (PLSD) comparisons revealed that women in G and S conditions performed comparably ($P > 0.50$) but significantly worse than women in E and ND conditions (all P values < 0.02), which did not differ ($P > 0.50$).

These studies demonstrate that stereotype threat in women's math performance can be reduced, if not eliminated, when women are presented with experiential accounts of the origins of stereotypes. People appear to habitually think of some sex differences in genetic terms unless they are explicitly provided with experiential arguments. It remains to be seen whether the results generalize to stereotypes about other groups and abilities.

Whether there are innate sex differences in math performance remains a contentious question. However, merely considering the role of genes in math performance can have some deleterious consequences. These findings raise discomforting questions regarding the effects that scientific theories can have on those who learn about them and the obligation that scientists have to be mindful of how their work is interpreted. What President Summers perhaps intended to be a provocative call for more empirical research on biological bases of achievement may inadvertently exacerbate the gender gap in science through stereotype threat.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5798/435/DC1
Materials and Methods

9 June 2006; accepted 15 August 2006
10.1126/science.1131100

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Correcting Quantum Errors with Entanglement

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We show how entanglement shared between encoder and decoder can simplify the theory of quantum error correction. The entanglement-assisted quantum codes we describe do not require the dual-containing constraint necessary for standard quantum error–correcting codes, thus allowing us to "quantize" all of classical linear coding theory. In particular, efficient modern classical codes that attain the Shannon capacity can be made into entanglement-assisted quantum codes attaining the hashing bound (closely related to the quantum capacity). For systems without large amounts of shared entanglement, these codes can also be used as catalytic codes, in which a small amount of initial entanglement enables quantum communication.

Entanglement plays a central role in quantum information processing. It enables the teleportation of quantum states without physically sending quantum systems (*1*), it doubles the capacity of quantum channels for sending classical information (*2*), and it is known to be necessary for the power of quantum computation (*3*, *4*). We show how shared entanglement provides a simpler and more fundamental theory of quantum error correction.

The theory of quantum error–correcting codes (QECCs) was established a decade ago as the primary tool for fighting decoherence in quantum computers and quantum communication systems. The first nine-qubit single-error–correcting code was a quantum analog of the classical repetition code, which stores information redundantly by duplicating each bit several times (*5*). Probably the most striking development in quantum error–correction theory is the use of the stabilizer formalism (*6*–*9*), whereby quantum codes are subspaces ("code spaces") in Hilbert space and are specified by giving the generators of an abelian subgroup of the Pauli group, called the stabilizer of the code space. Essentially, all QECCs developed to date are stabilizer codes. The problem of finding QECCs was reduced to that of constructing classical dual-containing quaternary codes (*6*). When binary codes are viewed as quaternary, this amounts to the well-known Calderbank-Shor-Steane construction (*10*, *11*). The requirement that a code contain its dual is a consequence of the need for a commuting stabilizer group. The virtue of this approach is that we can directly construct quantum codes from classical codes with a certain property, rather than having to develop a completely new theory of quantum error correction from scratch. Unfortunately, the need for a self-orthogonal parity check matrix presents a substantial obstacle to importing the classical theory in its entirety, especially in the context of modern codes such as low-density parity check (LDPC) codes (*12*).

Assume that the encoder Alice and decoder Bob have access to shared entanglement. We will argue that in this setting every quaternary (or binary) classical linear code, not just dual-containing codes, can be transformed into a QECC, and we illustrate this with a particular example. If the classical codes are not dual-containing, they correspond to a set of stabilizer generators that do not commute; however, if shared entanglement is an available resource, these generators may be embedded into larger, commuting generators, giving a well-defined code space. We call this the entanglement-assisted stabilizer formalism, and the codes constructed from it are entanglement-assisted QECCs (EAQECCs).

Standard Stabilizer Formalism

The power of the stabilizer formalism comes from the clever use of group theory. Let Π denote the set of Pauli operators $\{I, X, Y, Z\}$, and let $\Pi^n = \{I, X, Y, Z\}^{\otimes n}$ denote the set of n-fold tensor products of single-qubit Pauli operators. Then Π^n together with the possible overall factors ± 1, $\pm i$ forms a group G_n under multiplication, the n-fold Pauli group. Here are a few useful properties of the n-fold Pauli group: (i) Every element of G_n squares to $\pm I_n$ (plus or minus the identity), (ii) any two elements of G_n either commute or anti-commute, (iii) every element of G_n is unitary, and (iv) elements of G_n are either Hermitian or anti-Hermitian. The connection of G_n to error correction is straightforward: The elements of G_n can be identified as possible sets of errors that might affect a quantum register of n qubits.

Suppose $\mathcal{S}$ is an abelian subgroup of G_n. We define the stabilizer code $C(\mathcal{S})$ associated with $\mathcal{S}$ to be $C(\mathcal{S}) = \{|\psi\rangle: M|\psi\rangle = |\psi\rangle, \forall M \in \mathcal{S}\}$. The code $C(\mathcal{S})$ is the subspace fixed by $\mathcal{S}$, so $\mathcal{S}$ is called the stabilizer of the code. In other words, the code space is the simultaneous $+1$ eigenspace of all elements of $\mathcal{S}$. For an $[[n, k]]$ stabilizer code, which encodes k logical qubits into n physical qubits, $C(\mathcal{S})$ has dimension 2^k and $\mathcal{S}$ has 2^{n-k} elements (*9*). We should notice that for group $\mathcal{S}$ to be the stabilizer of a nontrivial subspace, it must satisfy two conditions: The elements of $\mathcal{S}$ commute, and $-I_n$ is not in $\mathcal{S}$. (This second condition implies that all elements of $\mathcal{S}$ are Hermitian and hence have eigenvalues ± 1.)

A group $\mathcal{S}$ can be specified by a set of independent generators, $\{M_i\}$. These are elements in $\mathcal{S}$ that cannot be expressed as products of each other and such that each element of $\mathcal{S}$ can be written as a product of elements from the set. If an abelian subgroup $\mathcal{S}$ of G_n has 2^{n-k} distinct elements up to an overall phase, then there are $n - k$ independent generators. The benefit of using generators is that it provides a compact representation of the group; to see whether a particular vector $|\psi\rangle$ is stabilized by a group $\mathcal{S}$, we need only check whether $|\psi\rangle$ is stabilized by these generators of $\mathcal{S}$.

Suppose $C(\mathcal{S})$ is a stabilizer code, and the quantum register is subject to errors from an error set $\mathcal{E} = \{E_a\} \subset G_n$. How are the error-correcting properties of $C(\mathcal{S})$ related to the generators of $\mathcal{S}$? First, suppose that E_a anti-commutes with a particular stabilizer generator M_i of $\mathcal{S}$. Then $M_i E_a|\psi\rangle = -E_a M_i|\psi\rangle = -E_a|\psi\rangle$.

$E_a|\psi\rangle$ is an eigenvector of M_i with eigenvalue -1 and hence must be orthogonal to the code space (all of whose vectors have eigenvalue $+1$). As the error operator E_a takes the code space of $C(\mathcal{S})$ to an orthogonal subspace, an occurrence of E_a can be detected by measuring M_i. For each generator M_i and error operator E_a, we can define a coefficient $s_{i,a} \in \{0, 1\}$, depending on whether M_i and E_a commute or anti-commute $M_i E_a = (-1)^{s_{i,a}} E_a M_i$.

The vector $\vec{s}_a = (s_{1,a}, s_{2,a}, \cdots, s_{n-k,a})$ represents the syndrome of the error E_a. In the case of a nondegenerate code, the error syndrome is distinct for all $E_a \in \mathcal{E}$, so that measuring the $n - k$ stabilizer generators will diagnose the error completely. However, a uniquely identifiable error syndrome is not always required for an error to be correctable.

What if E_a commutes with the generators of $\mathcal{S}$? If $E_a \in \mathcal{S}$, we do not need to worry, because the error does not corrupt the space at all. The real danger comes when E_a commutes with all the elements of $\mathcal{S}$ but is not itself in $\mathcal{S}$. The set of elements in G_n that commute with all of $\mathcal{S}$ is the centralizer $\mathcal{Z}(\mathcal{S})$ of $\mathcal{S}$. If $E \in \mathcal{Z}(\mathcal{S}) - \mathcal{S}$, then E changes elements of $C(\mathcal{S})$ but does not take them out of $C(\mathcal{S})$. Thus, if $M \in \mathcal{S}$ and $|\psi\rangle \in C(\mathcal{S})$, then $ME|\psi\rangle = EM|\psi\rangle = E|\psi\rangle$.

Because $E \notin \mathcal{S}$, there is some state of $C(\mathcal{S})$ that is not fixed by E. E will be an undetectable error for this code. Putting these cases together, a stabilizer code $C(\mathcal{S})$ can correct a set of errors $\mathcal{E}$ if and only if $E_a^\dagger E_b \in \mathcal{S} \cup [G_n - \mathcal{Z}(\mathcal{S})]$ for all $E_a, E_b \in \mathcal{E}$.

Entanglement-Assisted Stabilizer Codes

We will now illustrate the idea of the entanglement-assisted stabilizer formalism by an example. We

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know from the previous paragraph that a stabilizer code can be constructed from a commuting set of operators in G_n. What if we are given a noncommuting set of operators? Can we still construct a QECC? Let $\mathcal{S}$ be the group generated by the following noncommuting set of operators:

$$\begin{array}{llll} M_1 = Z & X & Z & I \\ M_2 = Z & Z & I & Z \\ M_3 = X & Y & X & I \\ M_4 = X & X & I & X \end{array} \qquad (1)$$

It is easy to check the commutation relations of this set of generators: M_1 anti-commutes with the other three generators, M_2 commutes with M_3 and anti-commutes with M_4, and M_3 and M_4 anti-commute. We will begin by finding a different set of generators for $\mathcal{S}$ with a particular class of commutation relations. We then relate $\mathcal{S}$ to a group $\mathfrak{B}$ with a particularly simple form and discuss the error-correcting conditions using $\mathfrak{B}$. Finally, we relate these results back to the group $\mathcal{S}$.

To see how this works, we need two lemmas. [See the supporting online material (SOM) for proofs.] The first lemma shows that there exists a new set of generators for $\mathcal{S}$ such that $\mathcal{S}$ can be decomposed into an "isotropic" subgroup $\mathcal{S}_I$ generated by a set of commuting generators and a "symplectic" subgroup $\mathcal{S}_S$ generated by a set of anti-commuting generator pairs (*13*).

Lemma 1. Given any arbitrary subgroup $\mathcal{V}$ in G_n that has 2^m distinct elements up to overall phase, there exists a set of m independent generators for $\mathcal{V}$ of the form $\{\overline{Z}_1, \overline{Z}_2, \cdots, \overline{Z}_\ell, \overline{X}_1, \cdots, \overline{X}_{m-l}\}$ where $m/2 \leq \ell \leq m$, such that $[\overline{Z}_i, \overline{Z}_j] = [\overline{X}_i, \overline{X}_j] = 0$, for all i, j; $[\overline{Z}_i, \overline{X}_j] = 0$, for all $i \neq j$; and $\{\overline{Z}_i, \overline{X}_i\} = 0$, for all i. Here $[A, B]$ is the commutator and $\{A, B\}$ the anti-commutator of A with B. Let $\mathcal{V}_I = \langle \overline{Z}_{m-\ell+1}, \cdots, \overline{Z}_\ell \rangle$ denote the isotropic subgroup generated by the set of commuting generators, and let $\mathcal{V}_S = \langle \overline{Z}_1, \cdots, \overline{Z}_{m-\ell}, \overline{X}_1, \cdots, \overline{X}_{m-\ell} \rangle$ denote the symplectic subgroup generated by the set of anti-commuting generator pairs. Then, with slight abuse of the notation, $\mathcal{V} = \langle \mathcal{V}_I, \mathcal{V}_S \rangle$ indicates that $\mathcal{V}$ is generated by subgroups $\mathcal{V}_I$ and $\mathcal{V}_S$.

For the group $\mathcal{S}$ that we are considering, one such set of independent generators is

$$\begin{array}{llll} \overline{Z}_1 = Z & X & Z & I \\ \overline{X}_1 = Z & Z & I & Z \\ \overline{Z}_2 = Y & X & X & Z \\ \overline{Z}_3 = Z & Y & Y & X \end{array} \qquad (2)$$

so that $\mathcal{S}_S = \langle \overline{Z}_1, \overline{X}_1 \rangle$, $\mathcal{S}_1 = \langle \overline{Z}_2, \overline{Z}_3 \rangle$, and $\mathcal{S} = \langle \mathcal{S}_I, \mathcal{S}_S \rangle$.

The choice of the notation $\overline{Z}_i$ and $\overline{X}_i$ is not accidental: These generators have exactly the same commutation relations as a set of Pauli operators Z_i and X_i on a set of qubits labeled by i. Let $\mathfrak{B}$ be the group generated by the following set:

$$\begin{array}{llll} Z_1 = Z & I & I & I \\ X_1 = X & I & I & I \\ Z_2 = I & Z & I & I \\ Z_3 = I & I & Z & I \end{array} \qquad (3)$$

From the previous lemma, $\mathfrak{B} = \langle \mathfrak{B}_I, \mathfrak{B}_S \rangle$, where $\mathfrak{B}_S = \langle Z_1, X_1 \rangle$ and $\mathfrak{B}_I = \langle Z_2, Z_3 \rangle$. Therefore, groups $\mathfrak{B}$ and $\mathcal{S}$ are isomorphic, which is denoted as $\mathfrak{B} \cong \mathcal{S}$. We can then relate $\mathcal{S}$ to the simpler group $\mathfrak{B}$ by the following lemma (*14*):

Lemma 2. If $\mathfrak{B} \cong \mathcal{S}$, then there exists a unitary U such that for all $B \in \mathfrak{B}$ there exists an $S \in \mathcal{S}$ such that $B = U S U^{-1}$ up to an overall phase.

As a consequence of this lemma, the error-correcting powers of $C(\mathfrak{B})$ and $C(\mathcal{S})$ are also related by a unitary transformation. In what follows, we will use $\mathfrak{B}$ to discuss the error-correcting conditions and then translate the results back to $\mathcal{S}$.

What is the code space $C(\mathfrak{B})$ described by $\mathfrak{B}$? Because $\mathfrak{B}$ is not a commuting group, the usual definition of $C(\mathfrak{B})$ does not apply, as the generators do not have a common eigenspace. However, by extending the generators, we can find a new group that is commuting and for which the usual definition of code space can apply; the qubits of the codewords will be embedded in a larger space. Notice that we can append a Z operator at the end of Z_1, an X operator at the end of X_1, and an identity at the end of Z_2 and Z_3 to make $\mathfrak{B}$ abelian:

$$\begin{array}{llllll} Z_1' = & Z & I & I & I & Z \\ X_1' = & X & I & I & I & X \\ Z_2' = & I & Z & I & I & I \\ Z_3' = & I & I & Z & I & I \end{array} \qquad (4)$$

We assume that the four original qubits are possessed by Alice (the sender), and the additional qubit is possessed by Bob (the receiver) and is not subject to errors. Let $\mathfrak{B}_e$ be the extended group generated by $\{Z_1', X_1', Z_2', Z_3'\}$. We define the code space $C(\mathfrak{B})$ to be the simultaneous $+1$ eigenspace of all elements of $\mathfrak{B}_e$, and we can write it down explicitly in this case:

$$C(\mathfrak{B}) = \{|\Phi\rangle^{AB}|0\rangle\,|0\rangle\,|\Psi\rangle\} \qquad (5)$$

where $|\Phi\rangle^{AB}$ is a maximally entangled state shared between Alice and Bob, and $|\psi\rangle$ is an arbitrary single-qubit pure state. Because entanglement is used, this is an EAQECC. We use the notation $[[n, k; c]]$ to denote an EAQECC that encodes k qubits into n qubits with the help of c ebits. (Sometimes we will write $[[n, k, d; c]]$ to indicate that the "distance" of the code is d, meaning it can correct at least $\lfloor \frac{d-1}{2} \rfloor$ errors.) The number of ebits c needed for the encoding is equal to the number of anti-commuting pairs of generators in $\mathfrak{B}_S$. The number of ancilla bits s is equal to the number of independent generators in $\mathfrak{B}_I$. The number of encoded qubits k is equal to $n - c - s$, and we define the rate of the EAQECC to be $(k - c)/n$. Therefore, $C(\mathfrak{B})$ is a $[[4, 1; 1]]$ EAQECC with zero rate: $n = 4$, $c = 1$, $s = 2$, and $k = 1$. Note that the zero rate does not mean that no qubits are transmitted by this code! Rather, it implies that a number of bits of entanglement is needed that is equal to the number of bits transmitted. In general, $k - c$ can be positive, negative, or zero.

Now we see how the error-correcting conditions are related to the generators of $\mathfrak{B}$. We saw that if an error $E_a \otimes I^B$ anti-commutes with one or more of the operators in $\{Z_1', X_1', Z_2', Z_3'\}$, it can be detected by measuring these operators. This will only happen if the error E_a anti-commutes with one of the operators in the original set of generators $\{Z_1, X_1, Z_2, Z_3\}$, as the entangled bit held by Bob is assumed to be error-free. Alternatively, if $E_a \otimes I^B \in \mathfrak{B}_e$, or equivalently if $E_a \in \mathfrak{B}_I$, then E_a does not corrupt the encoded state. In this case, we call the code degenerate. Altogether, $C(\mathfrak{B})$ can correct a set of errors E_0 if and only if $E_a^\dagger E_b \in \mathfrak{B}_I \cup [G_4 - Z(\mathfrak{B})]$ for all $E_a, E_b \in \mathcal{E}_0$.

With this analysis of $\mathfrak{B}$, we can go back to determine the error-correcting properties of our original stabilizer $\mathcal{S}$. We can construct a QECC from a nonabelian group $\mathcal{S}$ if entanglement is available, just as we did for the group $\mathfrak{B}$. We add extra operators Z and X to make $\mathcal{S}$ abelian as follows:

$$\begin{array}{llllll} \overline{Z}_1' = & Z & X & Z & I & Z \\ \overline{X}_1' = & Z & Z & I & Z & X \\ \overline{Z}_2' = & Y & X & X & Z & I \\ \overline{Z}_3' = & Z & Y & Y & X & I \end{array} \qquad (6)$$

where the extra qubit is once again assumed to be possessed by Bob and to be error-free. Let $\mathcal{S}_e$ be the group generated by the above operators. Since $\mathfrak{B} \cong \mathcal{S}$, let U be the unitary from lemma 2. Define the code space $C(\mathcal{S})$ by $C(\mathcal{S}) = U^{-1}[C(\mathfrak{B})]$, where the unitary U is applied only on Alice's side. This unitary U can be interpreted as the encoding operation of the EAQECC defined by $\mathcal{S}$. Observe that the code space $C(\mathcal{S})$ is a simultaneous eigenspace of all elements of $\mathcal{S}_e$. As in the analysis for $C(\mathfrak{B})$, the code $C(\mathcal{S})$ can correct a set of errors $\mathcal{E}$ if $E_a^\dagger E_b \in \mathcal{S}_I \cup [G_4 - Z(\mathcal{S})]$ for all $E_a, E_b \in \mathcal{E}$.

The algebraic description is somewhat abstract, so let us translate this into a physical picture. Alice wishes to encode a single ($k = 1$) qubit state $|\psi\rangle$ into four ($n = 4$) qubits and transmit them through a noisy channel to Bob. Initially, Alice and Bob share a single ($c = 1$) maximally entangled pair of qubits: one ebit. Alice performs the encoding operation U on her bit $|\psi\rangle$, her half of the entangled pair, and two ($s = 2$) ancilla bits. She then sends the four qubits through the channel to Bob. Bob measures the extended generators $\overline{Z}_1'$, $\overline{X}_1'$, $\overline{Z}_2'$, and

$\overline{Z}_3'$ on the four received qubits plus his half of the entangled pair. The outcome of these four measurements gives the error syndrome; as long as the error set satisfies the above requirement, Bob can correct the error and decode the transmitted qubit $|\psi\rangle$.

We have worked out the procedure for a particular example, but any EAQECC will function in the same way. The particular parameters n, k, c, and s will vary depending on the code. It should be noted that the first example of entanglement-assisted error correction produced a [[3, 1, 3; 2]] EAQECC based on the [[5, 1, 3]] standard QECC (*15*). Our construction differs in that it is completely general and, more important, eschews the need for commuting stabilizers.

Construction of EAQECCs from Classical Quaternary Codes

We will now examine the [[4, 1; 1]] EAQECC given above and show that it can be derived from a classical non–dual-containing quaternary [4, 2] code. This is a generalization of the well-known construction for standard QECCs (*16*).

First, note that this [[4, 1; 1]] code is nondegenerate and can correct an arbitrary one-qubit error. [Therefore the distance d of the code $C(S)$ is 3.] This is because the 12 errors X_i, Y_i, and Z_i, $i = 1, \ldots, 4$, have distinct nonzero error syndromes. X_i denotes the bit flip error on the i-th qubit, Z_i denotes the phase error on the i-th qubit, and Y_i means that both a bit flip and a phase flip error occur on the i-th qubit. It suffices to consider only these three standard one-qubit errors, because any other one-qubit error can be written as a linear combination of these three errors and the identity.

Next, we define the following map between the Pauli operators and elements of GF(4), the field with four elements:

Π	I	X	Y	Z
GF(4)	0	$\overline{\omega}$	1	ω

Note that under this map, addition in GF(4) corresponds to multiplication of the Pauli operators, up to an overall phase. So multiplication of two elements of G_n corresponds to the addition of two n vectors over GF(4), up to an overall phase.

The set of generators $\{M_i\}$ given in Eq. 1 is mapped to the matrix $\widetilde{H}_4$:

$$\widetilde{H}_4 = \begin{pmatrix} \omega & \overline{\omega} & \omega & 0 \\ \omega & \omega & 0 & \omega \\ \overline{\omega} & 1 & \overline{\omega} & 0 \\ \overline{\omega} & \overline{\omega} & 0 & \overline{\omega} \end{pmatrix} \quad (7)$$

Examining the matrix $\widetilde{H}_4$, we see that it can be written

$$\widetilde{H}_4 = \begin{pmatrix} \omega H_4 \\ \overline{\omega} H_4 \end{pmatrix} \quad (8)$$

where H_4 is the parity-check matrix of a classical [4, 2, 3] quaternary code whose rows are not orthogonal, and 3 is the minimum distance between codewords:

$$H_4 = \begin{pmatrix} 1 & \omega & 1 & 0 \\ 1 & 1 & 0 & 1 \end{pmatrix} \quad (9)$$

We get a [[4, 1, 3; 1]] EAQECC from a classical [4, 2, 3] quaternary code. This outperforms the best 4-bit self-dual QECC currently known, which is [[4, 0, 2]] (*16*). This connection between EAQECCs and quaternary classical codes is quite general (*17*). Given an arbitrary classical $[n, k, d]$ quaternary code, we can use Eq. 8 to construct a nondegenerate $[[n, 2k - n + c, d; c]]$ EAQECC. The rate becomes $(2k - n)/n$ because the $n - k$ classical parity checks give rise to $2(n - k)$ quantum stabilizer generators. (The complete details of this construction, along with rigorous proofs of its performance, can be found in the SOM.)

Discussion

Our entanglement-assisted stabilizer formalism enables us to construct QECCs from arbitrary classical quaternary codes without the dual-containing constraint. The simplification and unification that occur when entanglement assistance is allowed is an effect well known in the context of quantum Shannon theory (*18*, *19*).

The better the classical quaternary code is, the better the corresponding EAQECC will be. Searching for good quantum codes now becomes the problem of searching for good classical codes, which has been extensively studied and is well understood. Efficient modern codes, such as Turbo codes (*20*) or LDPC codes (*21*), whose performance approaches the classical Shannon limit, can now be used to construct corresponding quantum codes.

There are two interesting properties of EAQECCs constructed from Eq. 8. A classical quaternary code that saturates the Singleton bound will give rise to a quantum code saturating the quantum Singleton bound. To see this, assume that the classical $[n, k, d]$ quaternary code saturates the classical Singleton bound; that is, $n - k \geq d - 1$. The corresponding $[[n, 2k - n + c, d; c]]$ quantum code then saturates $n - (2k - n) = 2(n - k) \geq 2(d - 1)$ which is the quantum Singleton bound (*22*).

Another feature of EAQECCs is that a classical quaternary code that achieves the Shannon bound will give rise to a quantum code that achieves the "hashing" limit on a depolarizing channel (*23*). Let the rate (in base 4) R_C of a $[n, k, d]$ quaternary code meeting the Shannon bound of the quaternary symmetric channel be $R_C = C_4(f) = 1 - [H_4(f) + f \log_4 3]$, where f is the error probability and $H_b(f) = -f \log_b f - (1 - f) \log_b (1 - f)$ is the entropy in base b. Then the rate (in base 2) R_Q of the corresponding $[[n, 2k - n + c, d; c]]$ EAQECC is $R_Q = 2R_C - 1 = 1 - [H_2(f) + f \log_2 3]$, which is exactly the hashing bound on a depolarizing channel. The hashing bound is a lower bound on the closely related quantum channel capacity. It was previously achieved only by inefficient random coding techniques (*23*).

The use of an EAQECC requires an adequate supply of entanglement. However, these codes can be useful even if there is not a large amount of preexisting entanglement, by turning an EAQECC into a catalytic QECC (CQECC). The idea here is simple. Suppose the EAQECC has parameters n, k, c. Using c bits of preexisting entanglement, Alice encodes some of the qubits she wishes to transmit, plus one bit each from c maximally entangled pairs that she prepares locally. After her n bits have been transmitted to Bob and corrected and decoded, Bob has received $k - c$ qubits, plus c new bits of entanglement have been created. These can then be used to send another $k - c$ bits, and so on. The idea is that the perfect qubit channel that is simulated by the code is a stronger resource than preexisting entanglement (*19*). It is this catalytic mode of performance that makes the rate $(k - c)/n$ a reasonable figure of merit for an EAQECC as described above. Clearly the [[4, 1, 3; 1]] code described in this paper is useless as a catalytic code, though it is perfectly useful for an entanglement-assisted channel. To be a useful catalytic code, an EAQECC must have a positive value of $k - c$.

We have presented EAQECCs in a communication context up to now, but catalytic codes open the possibility of application to error correction in quantum computing, where we can think of decoherence as a channel into the future. In this case, the "seed" resource is not preexisting entanglement, but rather a small number of qubits that are error-free, either because they are physically isolated or because they are protected by a decoherence-free subspace or standard QECC.

CQECCs provide great flexibility in designing quantum communication schemes. For example, in periods of low usage, we can use an EAQECC in the catalytic mode to build up shared entanglement between Alice and Bob. Then in periods of peak demand, we can draw on that entanglement to increase the capacity. Quantum networks of the future can use schemes like this to optimize performance. In any case, the existence of practical EAQECCs will greatly enhance the power of quantum communications, as well as providing a beautiful connection to the theory of classical error-correction codes.

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24. We acknowledge helpful feedback from D. Poulin, G. Smith, and J. Yard. T.A.B. acknowledges financial support from NSF grant no. CCF-0448658, and T.A.B. and M.H.H. both received support from NSF grant no. ECS-0507270. I.D. and M.H.H. acknowledge financial support from NSF grant no. CCF-0524811 and NSF grant no. CCF-0545845.

Supporting Online Material

www.sciencemag.org/cgi/content/full/1131563/DC1
SOM Text

20 June 2006; accepted 31 August 2006
Published online 28 September 2006;
10.1126/science.1131563
Include this information when citing this paper.

Anisotropy and Corotation of Galactic Cosmic Rays

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The intensity of Galactic cosmic rays is nearly isotropic because of the influence of magnetic fields in the Milky Way. Here, we present two-dimensional high-precision anisotropy measurement for energies from a few to several hundred teraelectronvolts (TeV), using the large data sample of the Tibet Air Shower Arrays. Besides revealing finer details of the known anisotropies, a new component of Galactic cosmic ray anisotropy in sidereal time is uncovered around the Cygnus region direction. For cosmic-ray energies up to a few hundred TeV, all components of anisotropies fade away, showing a corotation of Galactic cosmic rays with the local Galactic magnetic environment. These results have broad implications for a comprehensive understanding of cosmic rays, supernovae, magnetic fields, and heliospheric and Galactic dynamic environments.

The anisotropy of Galactic cosmic rays (GCRs) may result from an uneven distribution of cosmic ray (CR) sources and the process of CR propagation in the Milky Way. CRs with energy below 10^{15} eV are accelerated by diffusive magnetohydrodynamic (MHD) shocks (*1*–*4*) of supernova remnants (SNRs) and stellar winds. The discreteness of SNRs might lead to a CR anisotropy (*5*). However, in reality, GCRs must almost completely lose their original directional information; their orbits are deflected by the Galactic magnetic field (GMF) and are randomized by irregular GMF components, having traveled on average for many millions of years, some also having interacted with interstellar gas atoms and dust. The transport of CRs in a magnetized plasma is governed by four major processes: convection, drift, anisotropic diffusion, and adiabatic energy change (deceleration or acceleration) (*6*, *7*). High-precision measurement of the CR anisotropy provides a means to explore magnetic field structures and provides insight for the CR transport parameters (*8*). The long-term high-altitude observation at the Tibet Air Shower Arrays (referred to as the Tibet ASγ experiment) has accumulated tens of billions of CR events in the multi-TeV energy range, ready for an unprecedented high-precision measurement of the CR anisotropy as well as the temporal and energy dependence of the CR anisotropy.

An expected anisotropy is caused by the relative motion between the observer and the CR plasma, known as the Compton-Getting (CG) effect (*9*), with CRs of greater intensity arriving from the direction of motion and those of less intensity arriving from the opposite direction. Such a CR anisotropy, caused by Earth's orbital motion around the Sun, has indeed been detected (*10*, *11*). Data assembled up until the 1930s (*9*) were consistent with a scenario that the CR plasma stays at rest in an inertial frame of reference attached to the Galactic center. If this were true, the Galactic rotation in the solar neighborhood might then be measurable. Nevertheless, such CR anisotropy due to the solar system rotation around the Galactic center at a speed of ~220 km s^{-1} remained inconclusive for more than seven decades. Now our high-precision two-dimensional (2D) measurement gives strong evidence for excluding the CR anisotropy of this origin and thus show a corotation of GCRs with the local GMF environment.

Historically, the GCR anisotropy (*12*, *13*) has been measured as the sidereal time variation at the spinning Earth, using both underground μ detectors and ground-based air shower arrays (*14*–*19*). Located at different geographic latitudes and operating in different years with various threshold energies, each individual experiment could only measure the CR

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modulation profile along the right ascension (R.A.) direction, which was usually fitted by the first few harmonics. Instead of using sine or cosine harmonics, one may introduce two Gaussian functions with declination (Dec)–dependent parameters (mean, width, and amplitude) to fit the so-called "tail-in" and "loss-cone" features and to obtain a tentative 2D anisotropic picture (*20*, *21*) by simultaneously fitting different experimental data. The CR deficiency was thought to be associated with a magnetic conelike structure and was thus named "loss-cone," whereas the CR enhancement is roughly in the direction of the heliospheric magnetotail and is thus referred to as "tail-in" enhancement (*12*, *13*). However, the spatial and energy dependence of CR anisotropy could not be determined accurately (*22*), and some subtle features remain hard to detect because the CR anisotropy appears more complex and cannot be properly described by two Gaussian functions. The Tibet AS-γ experiment alone can achieve 2D measurement in various energy ranges and can provide details of the 2D CR anisotropy.

The Tibet Air Shower Array experiment. The Tibet Air Shower Array experiment has been conducted at Yangbajing (90.522 E, 30.102 N; 4300 m above sea level) in Tibet, China, since 1990. In 1994, the Tibet I array (*23*)—consisting of 49 scintillation counters and forming a 7 by 7 matrix with a 15-m span—was expanded to become the Tibet II array, with an area of 36,900 m^2, by increasing the number of counters. In 1996, part of Tibet II with an area of 5175 m^2 was upgraded to a high-density (HD) array with a 7.5-m span (*24*). To increase the event rate, the HD array was enlarged in 1999 to cover the central part of the Tibet II array and became the Tibet III array (*25*–*27*). The area of the Tibet III array has reached 22,050 m^2. The trigger rates are ~105 Hz and ~680 Hz for the Tibet HD and III arrays, respectively. The data were acquired by running the HD array for 555.9 live days (the cumulative time when the array is waiting for selection of new CR events) from February 1997 to September 1999 and the Tibet III array for 1318.9 live days from November 1999 to October 2005. GCR events are selected for inclusion if any four-fold coincidence occurs in the counters with each recording more than 0.8 particles in charge, if the air shower core position is located in the array, and if the zenith angle of arrival direction is ≤40°. With all those criteria, both Tibet HD and III arrays have the modal energy of 3 TeV and a moderate energy resolution; the ~0.9° angular resolution estimated from Monte Carlo simulations (*28*, *29*) was verified by measuring the Moon shadow of CRs (*25*–*27*). In total, ~37 billion CR events are used in our data analysis.

Data analysis and results. With such a large data sample, we conducted a 2D measurement to reveal detailed structural information of the large-scale GCR anisotropy beyond the simple R.A. profiles. For each short time step (e.g., 2 min), the relative CR intensity at points in each zenith angle belt can be compared, and this comparison can be extended step by step to all points in the surveyed sky [see (*30*) for details of data analysis]. Lacking the absolute detector efficiency calibration in the Dec direction, absolute CR intensities along different Dec directions cannot be compared. Thus, the average intensity in each narrow Dec belt is normalized to unity. Our analysis procedure would give a correct 2D anisotropy if there is no variation in the average CR intensity for different Dec. We systematically examined the CR anisotropy in four different time frames: solar time for solar modulation, sidereal time for Galactic modulation, antisidereal time, and extended-sidereal time for systematic studies; we found systematic variations to be unimportant because CR intensity variations of the latter two (not shown) are not consistent with statistical fluctuations.

To study the temporal variation of CR modulation, we divided the data sample into two subsets. The first subset is from February 1997 to October 2001, covering the 23rd solar maximum (a period of a few years when solar magnetic activity is strongest); the second subset is from December 2001 to November 2005, approaching the solar minimum (a period of a few years when solar magnetic activity becomes minimal). Comparing the sidereal time plots for these two intervals (Fig. 1, A to C) shows that the CR anisotropy is fairly stable and insensitive to solar activity. The tail-in and loss-cone anisotropy components (*12*, *13*), extracted earlier from a combination of the underground μ telescope data analyses (*20*, *21*), are seen in our 2D plots in much finer detail and with a high accuracy (Fig. 1, A and B). Our new high-

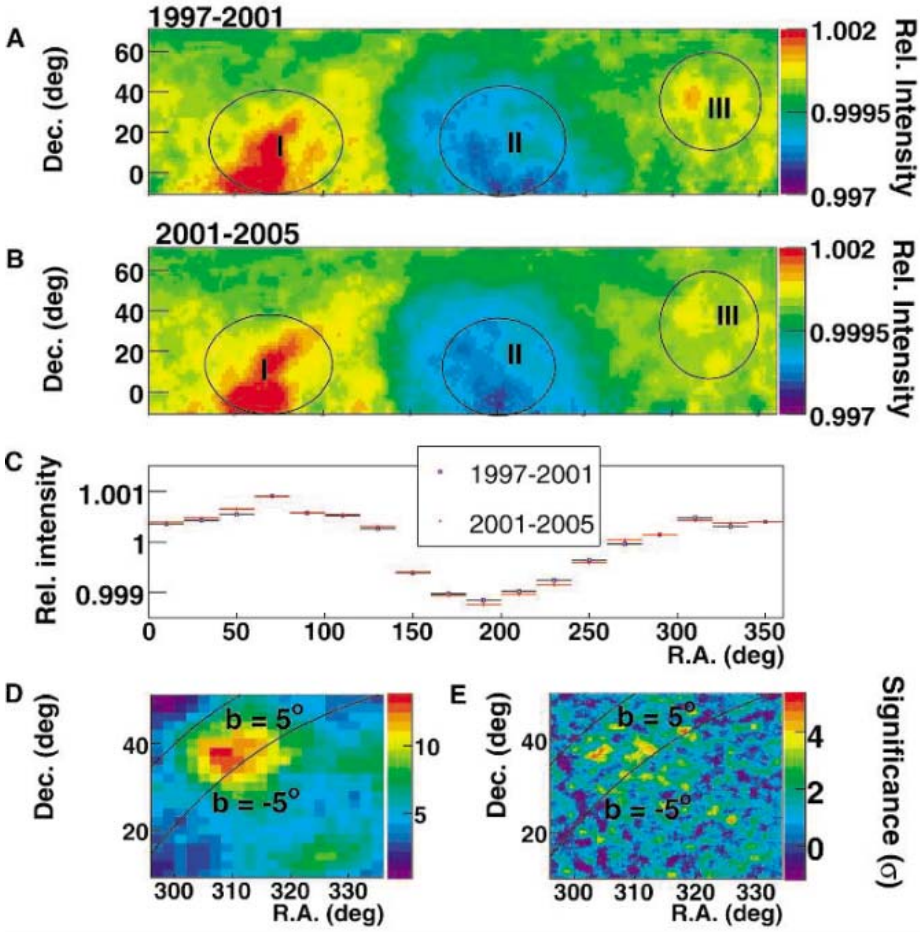

Fig. 1. Celestial CR intensity map for Tibet ASγ data taken from (**A**) 1997 to 2001 and (**B**) 2001 to 2005 (*40*). The vertical color bin width is 2.5 × 10^{-4} for the relative intensity in both (A) and (B). The circled regions labeled by I, II, and III are the tail-in component, the loss-cone component (*12*, *13*), and the newly found anisotropy component around the Cygnus region (~38°N Dec and ~309° R.A.), respectively. (**C**) The 1D projection of the 2D maps in R.A. for comparison. (**D**) and (**E**) show significance maps of the Cygnus region [pixels in radius of 0.9° and sampled over a square grid of side width 0.25° for (E)] for data from 1997 to 2005. The vertical color bin widths are 0.69 SD and 0.42 SD for significance in (D) and (E), respectively. Two thin curves in (D) and (E) stand for the Galactic parallel $b = \pm 5°$. Small-scale anisotropies (E) superposed onto the large-scale anisotropy hint at the extended gamma-ray emission.

precision measurement thus provides constraints on physical interpretations of these features.

Spreading across ~280° to ~360° in R.A., a new excess component with a ~0.1% increase of the CR intensity that peaks at Dec ~38°N and R.A. ~309° in the Cygnus region is detected at a significance level of 13.3 SD with a 5° pixel radius (Fig. 1D). The Cygnus region, where complex features are revealed in broad wavelength bands of radio, infrared, x-rays, and gamma rays, is rich in candidate GCR sources. Recently, the first unidentified TeV gamma-ray source was discovered here by high-energy gamma-ray astronomy experiment (HEGRA) (*31*). This region, as observed by energetic gamma-ray experiment telescope (EGRET) (*32*), appears to be the brightest source of diffuse GeV gamma rays in the northern sky and contributes substantially to the diffuse TeV gamma-ray emission in the Galactic plane as observed by Milagro (*33*), which rejects 90% of CR background while retaining ~45% of gamma rays. Such gamma rays originate from the interaction of CRs with gas and dust. Using more stringent event selection criteria (*30*), a deeper view of the Cygnus region with a 0.9° pixel radius shows that the large-scale excess consists of a few spatially separated enhancements of smaller scale superposed onto a large-scale anisotropy (Fig. 1E); this small-scale (~2°) excess favors the interpretation that the extended gamma-ray emission from the Cygnus region contributes considerably to the overall excess in the region (*34*). Because our experiment cannot yet distinguish gamma rays from the charged CR background, we cannot tell how much of this excess can be attributed to gamma rays and how much, if any, is associated with charged CRs (*35*). Such a determination requires upgrading the Tibet Air Shower arrays for CR and gamma-ray discrimination.

The solar time CR modulation was also stable (Fig. 2). We found that including events with fewer than eight detector coincidences (lower energy events) resulted in much larger modulation amplitudes than those obtained when these events were excluded (higher energy events). To avoid this, high multiplicity events with coincident detector numbers ≥8 were adopted (Fig. 2). The observed dipole anisotropy agrees very well with the expected CG effect as a result of Earth's orbital motion around the Sun. Thus, heliospheric magnetic field and solar activity does not influence the multi-TeV CR anisotropy.

Because of the stable nature of the sidereal time modulation, data from different years were combined to examine the energy dependence of CR anisotropy. Figure 3 shows the variation of anisotropy for five groups of events according to their different primary energies. For primary energies below 12 TeV, the anisotropies show little dependence on energy, whereas above this level, anisotropies fade away, consistent with a CR isotropy of Karlsruhe Shower Core and Array Detector (KASCADE) (*17*) in the energy range of 0.7 to 6 petaelectronvolts (PeV). Contrary to the earlier suggestion (*13*), the tail-in component remains visible above 50 TeV in smaller regions. Because the multi-TeV GCRs, whose gyroradii are hundreds or thousands of astronomical units, are not affected by the heliospheric magnetic field, it is clear that the GMF must be responsible for both tail-in and loss-cone modulations.

As a result of diminishing GCR anisotropy at high energies, we can test the CG anisotropy caused by the orbital motion of the solar system around the Galactic center, which would peak at α (R.A.) = 315°, δ (Dec) = 49° and minimize at α = 135°, δ = –49°, with an amplitude of 0.35%. This would be a salient signal in a real 2D measurement. However, as explained earlier, the modulation along the Dec direction is partly lost. After applying the normalization procedure along each Dec belt, the expected CG anisotropy is distorted and apparently peaks at α = 315°, δ = 0° and forms a trough at around α = 135°, δ = 0° with a smaller amplitude of ~0.23% (Fig. 4). To avoid any contamination from the nonvanishing tail-in and loss-cone anisotropies (*12*, *13*) when the primary energy is ~300 TeV, the upper half of the surveyed CR intensity map (with Dec > 25°) is used to compare with the predicted Galactic CG effect of amplitude ~0.16%. The fitted anisotropy amplitude is 0.03% ± 0.03%, consistent with an isotropic CR intensity. Therefore, our observations exclude the existence of other unknown Galactic CG effect with a confidence level of ~5 SD, assuming the absence of canceling effects. The null result of the Galactic CG effect implies that GCRs corotate with the local GMF environment.

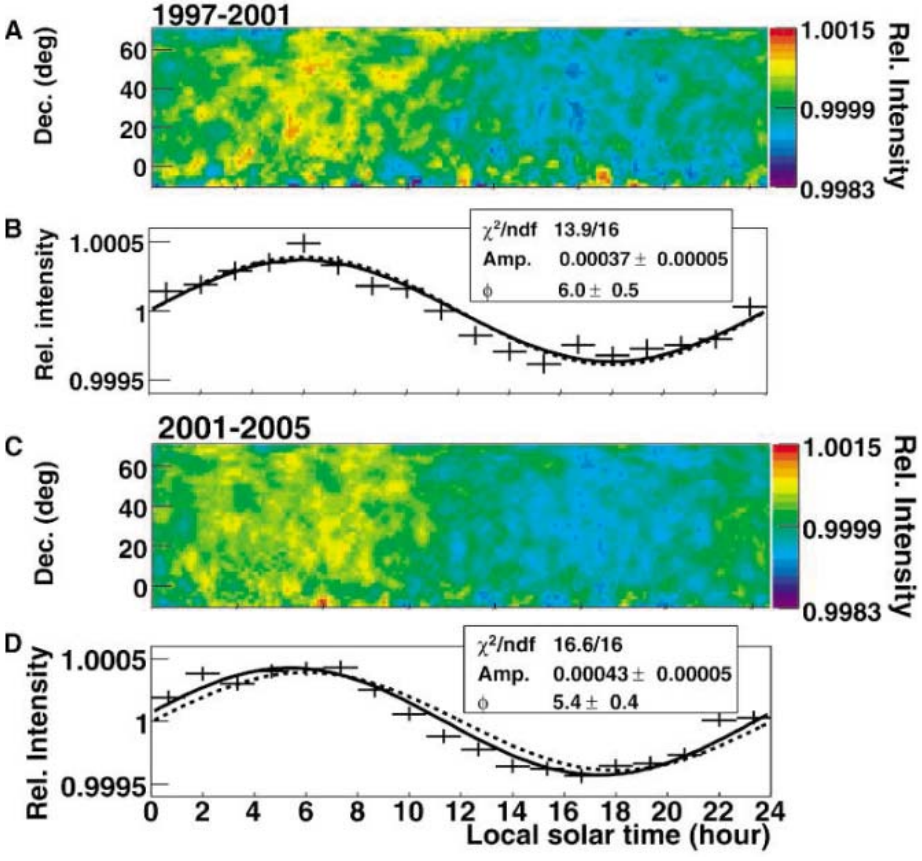

Fig. 2. Local solar time CR intensity map for the Tibet ASγ data taken from (**A** and **B**) 1997 to 2001 and (**C** and **D**) 2001 to 2005. Both samples have the modal energy of 10 TeV. The vertical color bin is 1.6×10^{-4} for the relative intensity in (A) and (C). In (B) and (D), the fitting function is in the form of Amp × cos[2π(*T* – ϕ)/24], where the local solar time *T* and ϕ are in units of hours and Amp is the amplitude. The χ^2 fit involves the number of degrees of freedom (ndf) given by the number of bins minus two, due to the two fitting parameters Amp and ϕ . The 1D plots are projections of the 2D maps in local solar time. In the 1D plots, the dashed lines are from the expected CG effect and the solid lines are the best harmonic fits, which agree well with the prediction. The solar time modulation appears stable and insensitive to solar activity.

Discussion. The observation of GCR anisotropy and diffuse gamma-ray emission plays an important role in probing sources and propagation of CRs. The detection of the new large-scale GCR anisotropy component and the indication

of extended gamma-ray emission from the same mysterious Cygnus region allow us to connect the GCR acceleration site and propagation. A precise spectral and morphological determination of the extended gamma-ray emission would be our next pursuit. The existence of large-scale GCR anisotropies up to a few tens of TeV indicates that they are not related to the heliospheric magnetic field. It is conceivable that GMF has large-scale structures in the heliospheric neighborhood.

As in many spiral galaxies, the Milky Way has large-scale differential rotations in stellar and magnetized gas disks with a GMF of a few μG. The GMF, GCRs, and thermal gas have similar energy densities of ~1 eV cm^{-3} and interact with each other dynamically. The corotation of the GCR plasma with the local GMF environment around the Galactic center is enforced by the Lorentz force as GCRs randomly scatter and drift in irregular GMF components (*36*). As the Galactic disk rotates differentially, the important inference is that the bulk GCR plasma within and above the Galactic disk must also rotate differentially. The GCR corotation evidence provides an important empirical basis for the study of Galactic MHD processes such as modeling synchrotron emission diagnostics for large-scale spiral structures of MHD density waves (*37*–*39*).

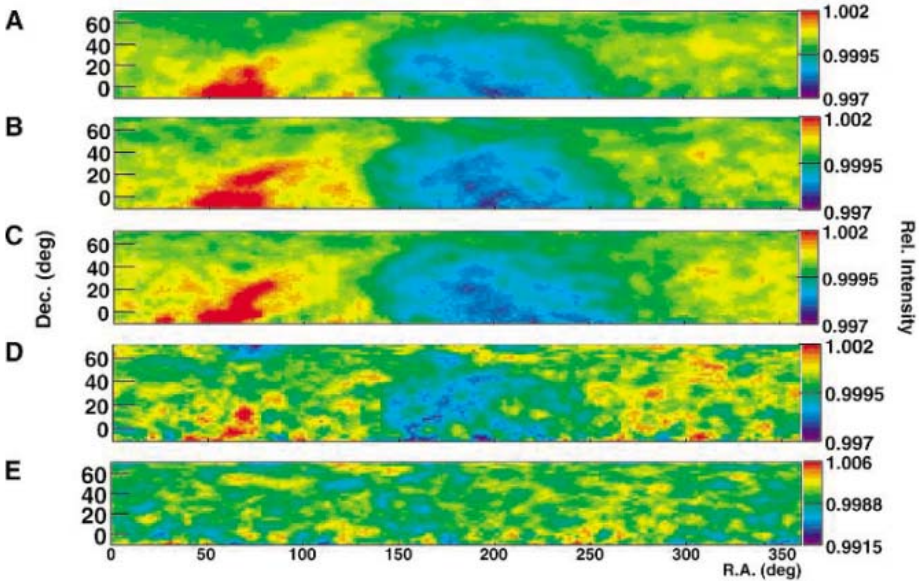

Fig. 3. Celestial CR intensity map for different representative CR energies. (**A**) 4 TeV; (**B**) 6.2 TeV; (**C**) 12 TeV; (**D**) 50 TeV; (**E**) 300 TeV. Data were gathered from 1997 to 2005. The vertical color bin width is 2.5 × 10^{-4} in [(A) to (D)] and 7.25 × 10^{-4} in (E) for different statistics, all for the relative CR intensity.

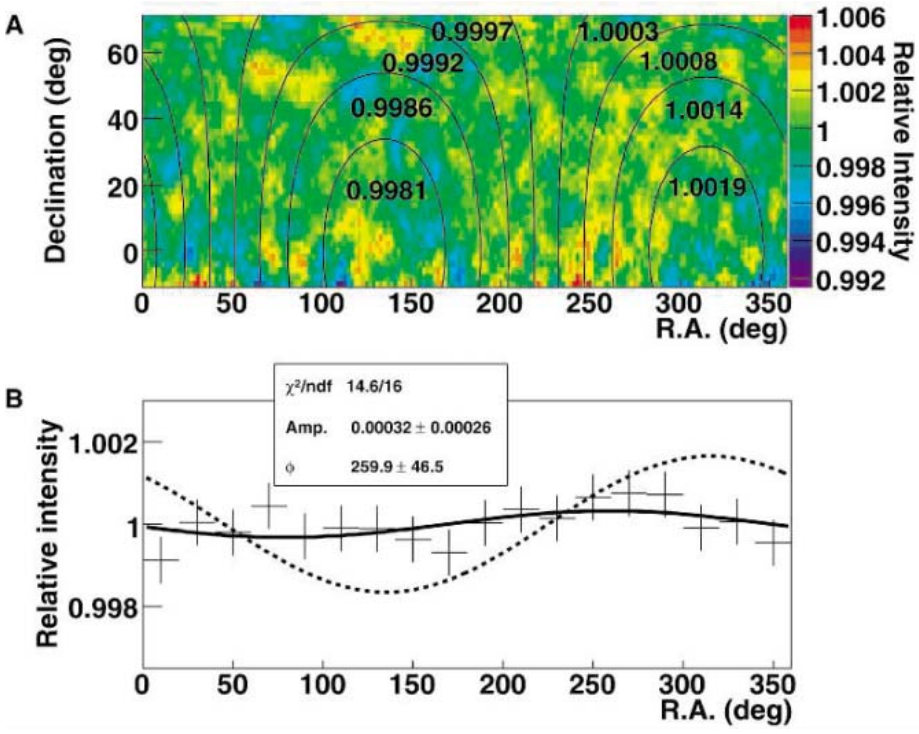

Fig. 4. Celestial or 2D local sidereal time CR intensity map and its 1D projection in the R.A. direction for 300 TeV CRs of all data. (**A**) The colored map is the same as Fig. 3E. The contours are the "apparent" 2D anisotropy expected from the Galactic CG effect. The width of the vertical color bin is 7.25 × 10^{-4} for the relative intensity in (A). The 1D projection is in map (**B**) for Dec between 25° and 70°, where the dashed line is the expected Galactic CG response and the solid line is the best fit to this observation using a first-order harmonic function. The fitting function is in the form of Amp × cos(R.A. − ϕ) where ϕ is in degrees and Amp is the amplitude. The χ^2 fit involves the ndf given by the number of bins minus two for the two fitting parameters Amp and ϕ. The data shows no Galactic CG effect with a confidence level of ~5 SD.

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40. Unless otherwise stated, images in Figs. 1 to 4 are presented using pixels in a radius of 5° and are sampled over a square grid of side width 2°; the modal energy is 3 TeV.
41. The collaborative experiment of the Tibet Air Shower Arrays has been performed under the auspices of the Ministry of Science and Technology of China and the Ministry of Foreign Affairs of Japan. This work was supported in part by Grants-in-Aid for Scientific Research on Priority Areas (712) (MEXT), by the Japan Society for the Promotion of Science, by the National Natural Science Foundation of China, and by the Chinese Academy of Sciences. The authors thank J. Kóta for reading the manuscript and for critical comments.

23 June 2006; accepted 22 September 2006
10.1126/science.1131702

Isolated Single-Cycle Attosecond Pulses

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We generated single-cycle isolated attosecond pulses around ~36 electron volts using phase-stabilized 5-femtosecond driving pulses with a modulated polarization state. Using a complete temporal characterization technique, we demonstrated the compression of the generated pulses for as low as 130 attoseconds, corresponding to less than 1.2 optical cycles. Numerical simulations of the generation process show that the carrier-envelope phase of the attosecond pulses is stable. The availability of single-cycle isolated attosecond pulses opens the way to a new regime in ultrafast physics, in which the strong-field electron dynamics in atoms and molecules is driven by the electric field of the attosecond pulses rather than by their intensity profile.

The past decade has seen remarkable advances in the field of femtosecond (1 fs = 10^{-15} s) light pulses with few optical cycles (*1*). The main achievements have been (i) the generation of ultrabroadband light pulses, directly from a laser oscillator or with the use of external spectral broadening mechanisms; (ii) the development of sophisticated techniques for dispersion compensation on ultrabroad bandwidths; (iii) the use of experimental methods for complete temporal characterization of ultrashort pulses, particularly frequency-resolved optical gating (FROG) (*2*) and spectral phase interferometry for direct electric field reconstruction (SPIDER) (*3*), in a number of different experimental implementations; and (iv) the generation of few-cycle light pulses with precisely controlled and reproducible electric field waveform [stabilized carrier-envelope phase (CEP)] (*4*–*6*). We show that these achievements can now be extended to the attosecond (1 as = 10^{-18} s) domain. We demonstrate the compression and the complete temporal characterization of isolated pulses with durations down to 130 as at 36-eV photon energy, which consist of less than 1.2 periods of the central frequency. This source of extreme ultraviolet (XUV) radiation lends itself as a tool to investigate basic electron processes in a spectral range approaching the energy level of the outermost electrons in atoms, molecules, and solid-state systems. The XUV source opens the way to a new regime in the applications of attosecond pulses in which a medium interacts with nearly single-cycle isolated attosecond pulses. Moreover, in this case it is appropriate to analyze the role of the CEP of the generated attosecond pulses. Using numerical simulations, we demonstrate that the carrier-envelope phase of the attosecond pulses is characterized by an excellent stability.

So far, isolated attosecond pulses with multiple optical cycles have been produced by selecting the high-energy (cut-off) harmonics (~90 eV) generated in neon by few-cycle (<7 fs) linearly polarized fundamental pulses with stabilized CEP (*7*–*9*). In this case, the minimum pulse duration of the XUV pulses is limited by the bandwidth of the selected cut-off harmonics (~10 eV), thus preventing the generation of single-cycle attosecond pulses. A different approach for the generation of broadband isolated attosecond pulses is based on the use of phase-stabilized few-cycle driving pulses in combination with the polarization gating technique (*10*–*13*). Such a method uses the strong dependence of the harmonic generation process on the ellipticity of the driving pulses in order to obtain a temporal window of linear polarization for the fundamental pulses. XUV generation is possible only during this temporal polarization gate, which can be shorter than half an optical cycle of the fundamental radiation. In combination with the use of few-cycle driving pulses with stable CEP, this technique allows the generation of broadband isolated attosecond pulses. The advantages of this method are (i) the generation of broadband XUV pulses; (ii) the broad tunability of the attosecond pulses upon changing the generating gas medium; (iii) energy scalability; and (iv) the possibility to access the single-cycle regime.

The generation of broadband attosecond pulses is an important tool for photoelectron spectroscopy. Although they are not Fourier limited (chirped pulses), broadband attosecond pulses can be used to measure attosecond electron dynamics just as effectively as if the pulses were transform limited (*14*). However, in this case a complete temporal characterization of the attosecond pulses is required. On the other hand, for a number of applications in which the temporal structure of the attosecond pulses is important, dispersion compensation is required in order to obtain pulses with duration close to the transform-limited value. To completely characterize the attosecond pulses in terms of temporal intensity and phase, we experimentally applied the method of FROG for complete reconstruction of attosecond burst (FROG CRAB, hereafter called CRAB) (*15*), an extension to attosecond electron wavepackets of the FROG method. When an atom is ionized by an XUV attosecond electric field in the presence of a streaking infrared (IR) pulse, the IR electric field acts as an ultrafast phase modulator on the generated electron wavepacket. The corresponding photo-ionization spectrum can be written as a FROG spectrogram with a pure phase gate $\phi(t)$ (*15*):

$$\Phi(t) = -\int_t^\infty dt'[\mathbf{v} \cdot \mathbf{A}(t') + \mathbf{A}^2(t')/2] \quad (1)$$

where $\mathbf{A}(t)$ is the vector potential of the IR field and $\mathbf{v}$ is the final electron velocity. A number of iterative algorithms can then be used to reconstruct the electric field of both the attosecond pulse and of the streaking IR pulse from the measured CRAB trace.

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We adjusted the CEP of the driving few-cycle light pulses [full-width at intensity half-maximum (FWHM): τ_D = 5 fs; central wavelength: λ_D = 750 nm] with controlled electric field in order to generate broadband and continuous XUV spectra in an Argon cell with static pressure, using the process of high-order harmonic generation (*16*, *17*). The required temporal modulation of the driving IR pulse polarization was obtained with the use of two birefringent plates [for a detailed description of the experimental apparatus, see the supporting online material (SOM) text]. Upon changing the CEP of the driving pulses, a clear transition from two emission bursts to a single emission burst was observed in the spectral domain (*13*). Using a grazing incidence toroidal mirror, we focused the attosecond pulses into an Argon gas jet. The streaking IR beam was spatially overlapped with the XUV beam in the gas jet. The generated photoelectrons were collected within an acceptance angle of ±2° around θ = 0, where θ is the angle between **v** and the polarization direction of the IR field.

Figure 1A shows a portion of an experimental CRAB trace, which represents the evolution of the photoelectron spectra as a function of the temporal delay between the XUV and the streaking IR pulses. The measured trace follows the evolution of the vector potential, **A**(*t*), of the streaking pulse. The temporal structure of the attosecond pulses was retrieved using the principal-component generalized projection algorithm (PCGPA) (*18*). In the reconstructed temporal intensity profile and phase of the XUV pulses (Fig. 1B), the pulse duration was 280 as (the Fourier limit is ~100 as), and the almost parabolic phase indicates the presence of a predominant second-order dispersion, corresponding to a positive linear chirp C ≅ 42 fs^{-2}. Such pulses correspond to only 2.5 optical cycles of the carrier frequency. The measured CRAB trace and the corresponding reconstruction of the XUV pulses clearly demonstrate the generation of isolated pulses, consistent with the measurement of a continuous XUV spectrum, with no clear evidences of harmonic peaks. The measured modulation of the width of the photoelectron spectrum was determined not only by the XUV pulse duration, but also by the chirp of the attosecond pulses (*15*). In our experimental conditions, the presence of positive chirp leads to a decrease of the electronic spectrum width (thus resulting in a spectral peak increase) in the temporal regions characterized by a negative slope of the vector potential, as clearly visible in Fig. 1A.

The measured positive chirp is intrinsic to the XUV generation process, because the harmonic emission time varies quasi-linearly with harmonic frequency (the spectral components at higher frequencies are emitted after those at lower frequencies) (*19*). As recently demonstrated in the case of trains of attosecond pulses (*20*), the positive chirp of the XUV radiation produced by high-order harmonic generation can be compensated for by the negative group delay dispersion of thin aluminum foils, which is almost constant on the bandwidth of the generated attosecond pulses. The CRAB trace reported in Fig. 1A was measured using a 100-nm-thick aluminum foil (on a nickel mesh) on the XUV beam, in order to filter out the fundamental radiation, thus reducing the intrinsic positive chirp of the attosecond pulses. To test the possibility of further compressing the XUV pulses, we used thicker aluminum foils. Figure 2A shows a complete CRAB trace measured with a 300-nm-thick aluminum foil. The retrieved CRAB trace

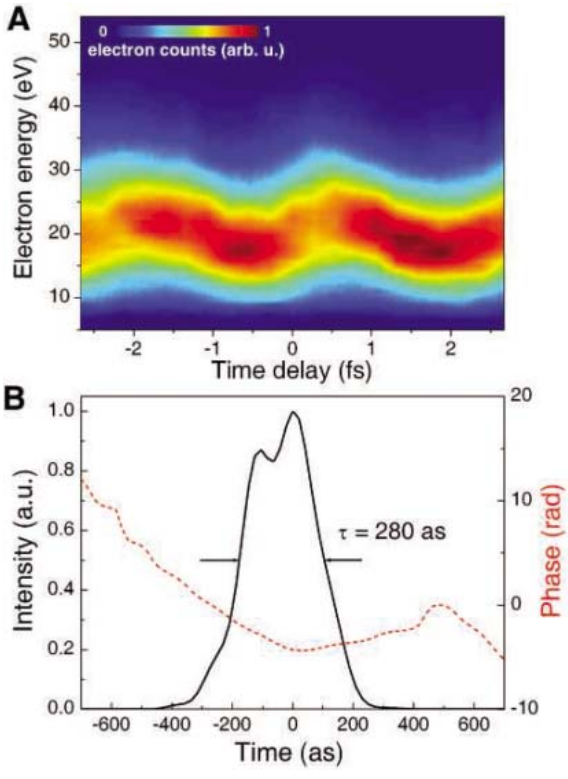

Fig. 1. (**A**) Portion of an experimental CRAB trace measured in the case of a 100-nm-thick aluminum foil as a function of the temporal delay between the attosecond and the streaking IR pulses. Isolated attosecond pulses were generated by phase-stabilized, 5-fs pulses with modulated polarization state. (**B**) Reconstruction of the temporal intensity profile and phase of the attosecond pulses obtained from the CRAB trace after 5 × 10^4 iterations of the PCGPA algorithm.

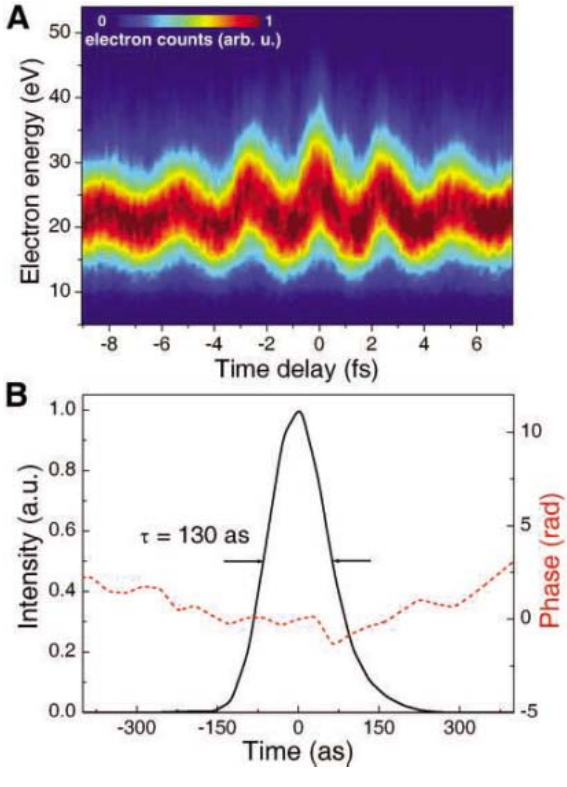

Fig. 2. (**A**) Complete experimental CRAB trace measured in the case of a 300-nm-thick aluminum foil as a function of the temporal delay between the attosecond and the streaking IR pulses. Isolated attosecond pulses were generated by phase-stabilized, 5-fs pulses with modulated polarization state. (**B**) Reconstruction of the temporal intensity profile and phase of the attosecond pulses obtained from the CRAB trace after 5 × 10^4 iterations of the PCGPA algorithm.

(Fig. 3) reproduces the experimental trace: The CRAB error, evaluated as the root mean square error per element of the trace (*21*), is $\sim 10^{-3}$. In the intensity profile and the temporal phase of the retrieved attosecond pulses (Fig. 2B), the pulse duration (FWHM) is 130 as, close to the Fourier limit, thus indicating a good compensation of the intrinsic chirp. Such pulses correspond to fewer than 1.2 optical cycles of the carrier frequency (*22*).

The single-cycle nature of the generated isolated pulses has important implications for ultrafast science and adds another parameter to the study of attosecond phenomena: the carrier-envelope phase of the isolated attosecond pulses. To address this topic, we modeled the physical processes involved in the attosecond pulse generation using the nonadiabatic saddle-point method (*23*, *24*). Such an approach is based on the concept of Feynman's path integrals (*23*, *25*), which correspond to the complex trajectories (quantum paths) followed by the electrons from the ionization instant to the recombination with the parent ion in the process of high-order harmonic generation. We verified that the results of the numerical simulations were in agreement with the experimental data. In particular, they perfectly reproduce the effects of the CEP of the driving pulses on the spectral properties of the harmonic radiation. Moreover, the calculated temporal characteristics of the attosecond pulses (such as pulse duration, temporal and spectral phase, and chirp) turn out to be in very good agreement with the results of the experimental CRAB reconstruction procedure.

Figure 4 shows the electric field evolution calculated with the same driving pulse parameters that were used in the experiment and considering the contribution of the aluminum foil: The calculated pulse duration is 135 as (FWHM of the intensity profile), in agreement with the experimental result. The numerical simulations allow us to analyze the role of the experimental parameters on the CEP of the attosecond pulses. We calculated the temporal evolution of the XUV electric field upon changing the CEP of the driving pulses. We varied the driving CEP values in a range of ~175 mrad, giving rise to an efficient generation of isolated attosecond pulses. As demonstrated in Fig. 4, which displays the calculated electric field evolution for two different values of the CEP of the driving pulses, the CEP of the isolated attosecond pulses is negligibly influenced by variation of the CEP of the driving pulses. The two pulses reported in Fig. 4 were temporally shifted to overlap their intensity envelopes; the same shift determines the overlap of the electric fields of the corresponding driving pulses (*26*). In the considered CEP range of the IR pulses, only one electron quantum path contributes in a relevant way to the XUV emission. Because the corresponding electron wavepacket is emitted around a stationary point of the intensity profile of the driving pulse (*12*), relative changes of the emission and recombination times with respect to the IR intensity envelope (due to different CEP values) do not significantly affect the phase accumulated by the electron wavepacket (*27*). This determines an intrinsic mechanism for stabilization of the electric field of the attosecond pulses against variations of the CEP of the driving pulses. We have analyzed the effects of fluctuations of the excitation intensity; in this case, the induced variation of the attosecond CEP is very small. Indeed, a 2% intensity fluctuation leads to a ~140-mrad CEP shift. The most important conclusion is that the CEP of the generated attosecond pulses is markedly stable. The attosecond CEP could be finely tuned, for example, by using aluminum foils with variable thickness: At 36 eV, a π CEP variation is induced by the addition of ~80 nm of aluminum (although in this case also the pulse duration is affected).

The intrinsic robustness of the stability of attosecond pulse CEP should lead to new applications in ultrafast physics. These results pave the way to theoretical and experimental studies for the determination of the exact electric field evolution of attosecond XUV pulses. As the energy of the generated attosecond pulses can be easily increased by increasing the energy of the IR driving pulses, we can envisage applications of the phase-stable single-cycle attosecond pulses to the study of strong-field electron dynamics in atoms and molecules, when processes are triggered and controlled by the electric field of the attosecond pulses, rather than by the intensity profile. As in the case of few-cycle IR pulses, we expect the possibility to influence and modify the ionization mechanisms of valence electrons upon changing the CEP of the attosecond pulses in the strong-field regime. In a lower intensity regime, as recently proposed in the case of few-cycle infrared pulses (*28*), the ultrafast dynamics of the population of bound and continuum states in atoms and molecules can be coherently influenced by the electric field temporal evolution of single-cycle attosecond pulses. The control of the CEP of such pulses provides an additional degree of freedom in the preparation and manipulation of atomic and molecular wavepackets. Another application is the investigation of photoionization processes in the presence of few-cycle XUV pulses and intense (>10^{13} W/cm^2) synchronized IR fields. In this case, electron wavepackets can be emitted in the continuum following two different ionization channels: multiphoton above-threshold ionization associated to the IR field and absorption of single XUV photons. The coherent superposition of the two ionization probabilities determines an interference pattern in the photoelectron spectra, which should offer the possibility to measure the CEP of the attosecond pulses. Moreover, the availability of few-cycle isolated pulses in the photon energy range of about 30 eV is particularly important for the study of electron dynamics in chemistry and molecular and solid state physics, in which a number of fundamental processes are related to the outermost electrons, directly accessible by the generated attosecond pulses. On the other hand, the possibility of generating single-cycle pulses of less than 100 as at higher energy with the use of the polarization gating method in neon (*13*) should allow the study of the coherent dynamics of inner-shell electrons with unprecedented temporal resolution.

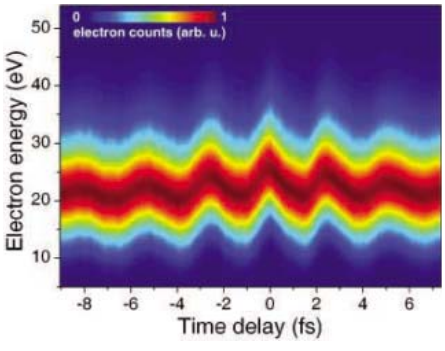

Fig. 3. Reconstruction of the CRAB trace of the attosecond pulses retrieved from the experimental trace shown in Fig. 2A, after 5×10^4 iterations of the PCGPA algorithm.

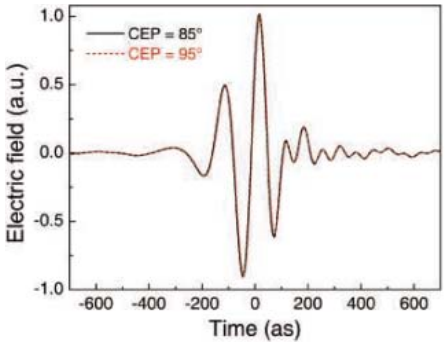

Fig. 4. Electric field of 135-as isolated pulses calculated for two different values of the CEP of the driving pulses with the use of the nonadiabatic saddle-point method. The simulations have been performed assuming the same driving pulse parameters that were used in the experiment.

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Supporting Online Material
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References

21 July 2006; accepted 11 September 2006
10.1126/science.1132838

Molecular Imaging Using a Targeted Magnetic Resonance Hyperpolarized Biosensor

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A magnetic resonance approach is presented that enables high-sensitivity, high-contrast molecular imaging by exploiting xenon biosensors. These sensors link xenon atoms to specific biomolecular targets, coupling the high sensitivity of hyperpolarized nuclei with the specificity of biochemical interactions. We demonstrated spatial resolution of a specific target protein in vitro at micromolar concentration, with a readout scheme that reduces the required acquisition time by >3300-fold relative to direct detection. This technique uses the signal of free hyperpolarized xenon to dramatically amplify the sensor signal via chemical exchange saturation transfer (CEST). Because it is ~10,000 times more sensitive than previous CEST methods and other molecular magnetic resonance imaging techniques, it marks a critical step toward the application of xenon biosensors as selective contrast agents in biomedical applications.

Magnetic resonance imaging (MRI) is established as a powerful method for tomography of opaque biological samples (*1*). However, its application in molecular imaging (determining the spatial distribution of specific molecules of interest) has been limited because of inherent low sensitivity (*2*). Conventional MRI techniques usually detect highly abundant nuclei, such as protons (^{1}H) of water (110 M ^{1}H concentration) and/or fat, to guarantee sufficient signal intensity despite the low thermal polarization. Contrast agents, including some that bind to specific biomolecular targets, have been developed that induce small but detectable changes in these strong signals. However, the required contrast agent concentration is ~0.5 to 2 mM for signal changes based on relaxation enhancements (*2*) or saturation transfer experiments (*3*). Application of exogenous ^{129}Xe circumvents limitations in sensitivity and contrast, because Xe nuclei can be hyperpolarized before transfer into the system of interest and their nuclear magnetic resonance (NMR) frequencies are extremely sensitive to the molecular environment. Hyperpolarization amplifies the available magnetization by a factor of $>10^4$, and it is currently used to increase anatomical contrast in MRI for imaging of void spaces such as the lung (*4*).

Detection of specific biomolecules in a solution environment can be accomplished by xenon biosensors, which trap Xe atoms in molecular cages that have been functionalized to bind the desired target (*5*, *6*). Xenon biosensors are composed of a cryptophane-A cage (*7*), a linker, and a targeting moiety (Fig. 1A), which can be an antibody or ligand that enables detection of a specific analyte. The cage-encapsulated xenon nuclei give rise to a unique signal that is well shifted from that of free Xe. Hence, these compounds act as selective imaging contrast agents for near-zero background MRI that benefit from the high specificity of biochemical targeting (*5*, *6*). The excellent resolution of free and biosensor-bound Xe was used recently to obtain a one-dimensional NMR profile from a bead-immobilized biosensor in a perfusion phantom that delivers Xe-saturated water to a test volume inside the NMR probe (*8*). This setup mimics in principle Xe delivery to a biosensor-labeled volume of interest as it would be provided by the blood stream in vivo after injection or inhalation. Direct application of the xenon biosensor to molecular imaging has been impaired by the fact that, for typical experiments, only ~1% of dissolved Xe is associated with the sensor (*9*). A further challenge was shown to lie in the broadening of sensor signal in heterogeneous samples (*8*, *9*), leading to a significant reduction in signal to noise.

Here, we introduce a different approach for obtaining MR images of Xe biosensors that is based on chemical exchange between the biosensor-encapsulated Xe and the easily detectable pool of free Xe (*10*), thus making optimized use of the available biosensor-associated magnetization. These Xe nuclei fulfill the conditions of slow exchange on the NMR time scale; that is, the frequency difference of the resonances ($\Delta\omega$) is large compared with the exchange rate (τ_{ex}^{-1}) between the two sites: $\Delta\omega \gg \tau_{ex}^{-1}$. Such exchange is used for signal amplification by measuring a decrease in the intense free xenon signal after selective saturation of the biosensor-bound xenon. Exchange-mediated depletion of the free xenon signal requires that the exchange rate be fast compared with the longitudinal relaxation time of free xenon ($\tau_{ex}^{-1} \gg T_1^{-1}$) and that the saturation be effective (transition rate $W \geq \tau_{ex}^{-1}$). With a value of $T_1 \approx 66$ s in water (*11*) at 9.4 T and exchange dynamics characterized by $\tau_{ex} \approx$ 40 ms (*10*), Xe nuclei in the sensor cages are ideal for saturation transfer.

The applied technique is similar to chemical exchange saturation transfer or CEST (*12*), which was previously developed for use with proton contrast agents. However, because the method presented here, HYPER-CEST, uses hyperpolarized nuclei with a long relaxation time, nearly the entire sensor-related magnetization depletion is stored in the observed signal.

This scheme allows substantial sensitivity improvement, which we demonstrated with two-dimensional images that were obtained in a few minutes of a biosensor solution sample with ~5 μM concentration of a recently described biosensor construct (*8*, *9*) that binds via its biotin moiety to avidin-functionalized agarose beads in an aqueous environment. The ^{129}Xe NMR spectra of such bead samples were composed of three different signals (Fig. 1A): free Xe in the bead medium resonates at $\delta_1 = 193.6$ parts per million (ppm) (referred to as "bead signal" in the following), free Xe in pure water at $\delta_2 = 192.5$ ppm, and Xe inside the biosensor cage at $\delta_3 = 65.4$ ppm (chemical shifts are

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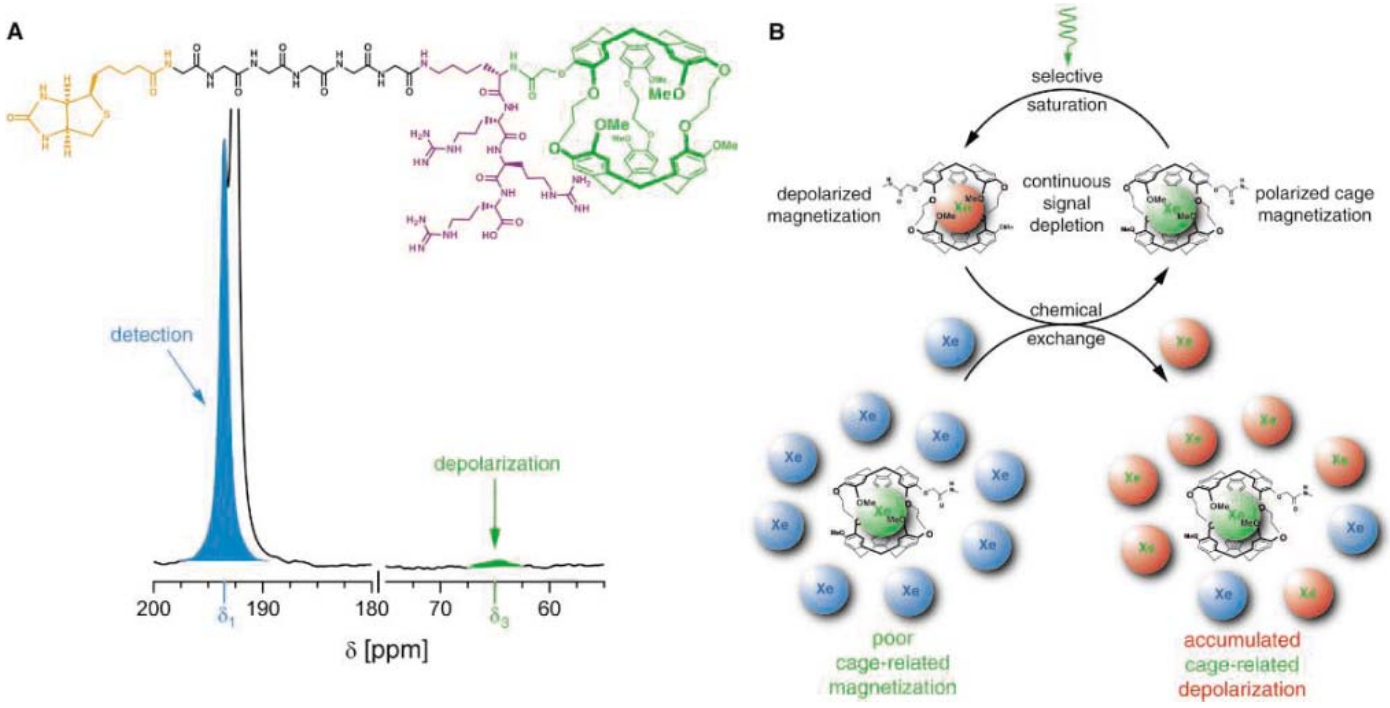

Fig. 1. Sensitivity-enhanced NMR detection of Xe biosensors. (**A**) Chemical structure of the Xe biosensor illustrating the cryptophane-A cage (green), the linker (black), the targeting moiety (biotin in this case, orange), and the peptide chain (purple) that is required for sufficient water solubility. The ^{129}Xe NMR spectrum of this construct at 50 μM bound to avidin agarose beads yields only a broad, weak resonance from encapsulated Xe at δ_3, even for 256 acquisitions. Chemical exchange with free Xe outside the cage (resonance δ_1) enables sensitivity enhancement by depolarizing the δ_3 nuclei and detecting at δ_1. (**B**) Amplifying the cage-related magnetization using HYPER-CEST. Selective saturation of biosensor-encapsulated Xe (green) and subsequent chemical exchange with the free Xe (blue) allows accumulation of depolarized nuclei (red). This procedure corresponds to continuous depolarization of cage-related magnetization that can be measured indirectly after several cycles by the difference between initial and final bulk magnetization.

calibrated relative to the Xe gas signal at δ = 0 ppm). Selective presaturation around δ_3 initiated the HYPER-CEST process (Fig. 1B) that accumulates selectively depolarized nuclei in a cyclic process (Fig. 1B). Because the depolarized magnetization M_z = 0 cannot be detected directly, the difference between MRI data sets with on- and off-resonant presaturation allows for sensitive detection of sample regions of dilute biosensor.

Chemical shift imaging (CSI) is an MRI method that preserves the intrinsic frequency information of NMR signals (*13*). It uses pulsed magnetic field gradients to generate phase-encoded signals in the frequency domain and provides maps of spatially resolved NMR spectra after two-dimensional Fourier transformation (FT). This method yields selective images for any spectral component. To demonstrate specificity of the biosensor imaging method, we embedded agarose beads in a flow system described previously (*8*) such that the volume of interest is divided into two compartments (Fig. 2A). Volume 2 contained avidin-agarose beads (*9*) with biosensor bound at a concentration of 5 μM, and volume 1 contained biosensor-free beads. The phantom was attached to an apparatus that provides perfusion with Xe-saturated water, as previously described (*8*). The concentration of detectable nuclei was equivalent to ~2 μM of 100% polarized xenon (~260 μM xenon with the natural 25% ^{129}Xe, polarized to P = 3%). Direct detection of the sensor at a concentration of 50 μM in volume 2 required signal averaging of 256 transients [signal-to-noise ratio (S/N) ~ 3.5, biosensor linewidth ~210 Hz, Fig. 1A]; therefore ~25,000 transients were necessary to directly observe the sensor at 5 μM even without any spatial resolution. Application of the sensitive HYPER-CEST technique enabled localized detection of this biosensor concentra-

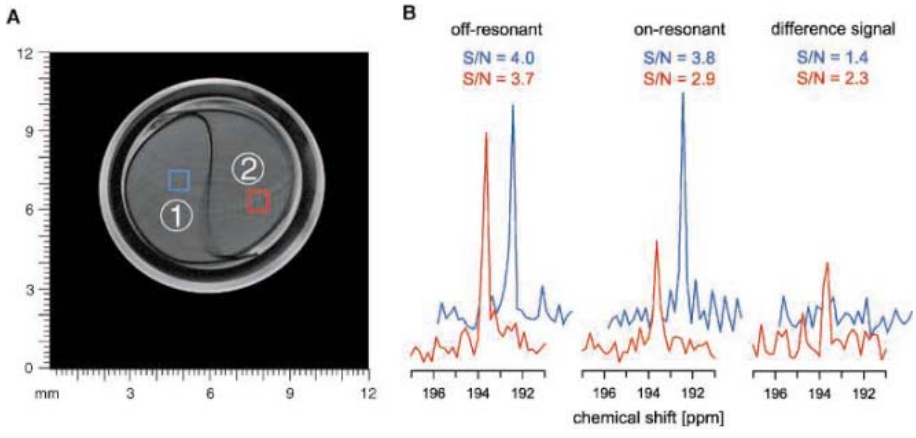

Fig. 2. Demonstration of HYPER-CEST on a two-compartment phantom. (**A**) Transverse ^{1}H NMR image of the two-compartment phantom containing avidin-agarose beads. The biosensor is only present in volume 2. Two voxels were selected to allow demonstration of saturation transfer: the red voxel as part of the sensor-marked volume and the blue voxel as part of the control compartment. (**B**) Localized ^{129}Xe NMR spectra (absolute signal) from the two voxels marked in (A). Undisturbed resonances from the bead-associated Xe in the biosensor-labeled volume (red) and the control volume (blue) are obtained for off-resonant cw saturation, whereas on-resonant saturation depletes the signal in compartment 2. The difference spectrum reveals signal only for resonances arising from species involved in the chemical exchange with the biosensor cage.

tion with only two complete CSI acquisitions (Materials and Methods).

The specificity of the HYPER-CEST effect to biosensor-containing regions is excellent (Fig. 2B). A reference spectrum is given for off-resonant 4-s continuous wave (cw) saturation at $\delta_{off} = \delta_1 + (\delta_1 - \delta_3) = \delta_1 + \Delta$. Switching the frequency to $\delta_{on} = \delta_1 - \Delta = \delta_3$ causes a significant depletion of the bead signal at δ_1 for 2, whereas the spectrum from volume 1 remains essentially unaffected. Hence, the Fourier transform of the difference raw data only contains bead signal for areas participating in the saturation transfer as a consequence of biosensor labeling.

The corresponding images in Fig. 3 illustrate the inherent multimodal contrast of our technique, i.e., imaging contrast provided by both the chemical shift information and the tunable HYPER-CEST effect. The data set with off-resonant presaturation displays the compartments that contain both types of beads when only the signal intensity at δ_1 is evaluated (Fig. 3A). This Xe image matches precisely the geometry seen in the conventional ^{1}H MR image in Fig. 2A. Additional information is given by plotting the signal distribution of the solution dissolved xenon peak, δ_2. It displays the surrounding outlet tube of the phantom (Fig. 3B), i.e., a volume that contains the perfusion agent but that does not contain the biosensor or its molecular target. These images show a near-zero background because of the good spectral discrimination of the signal components. On-resonant presaturation depletes the δ_1 signal in compartment 2, leaving the signal in compartment 1 undisturbed (Fig. 3C). The difference image for δ_1 (Fig. 3D) only contains signal from volume 2 where the biosensor is present. The solution signal remains nearly unaffected by switching the saturation frequency.

HYPER-CEST does not compete with relaxation of thermally polarized nuclei; i. e., there is no counteracting effect of repolarization as would be the case for the saturation of thermally polarized nuclei. Thus, the concentration of the detected nuclei can be even lower than that of the contrast agent, i.e., 2 μM versus 5 μM in our case; a comparison with conventional CEST applications shows the gain provided by the process of selective depletion. Using water protons as the detectable pool in conventional CEST requires large magnetic fields to decrease relaxation effects and increase the frequency difference to the saturated component. The latter problem was partially circumvented by incorporating paramagnetic ions in contrast agents, a technique called PARACEST (*3*). Because those agents have only one coordination site for water molecules, even relatively high concentrations (2 mM, i.e., 800 times more active sites than in this study) cause a signal decrease of no more than 4 to 12%, even when the concentration of polarized nuclei is 2600-fold higher (5.2 mM for water at 7 T) compared with our setup. A contrast comparable to the results reported here, i.e., a signal decrease of 40 to 50%, was observed with CEST by using exchangeable sites on macromolecules at 100 μM (*14*). However, those results for poly-L-lysine were based on concentrations of 700 mM for the exchangeable sites and 8.7 mM for the polarized nuclei (water at 11.7 T). Hence, the sensitivity gain given by HYPER-CEST provides the same contrast with only 1/140,000 of active sites and 1/4350 of detectable nuclei.

The results presented emphasize the high potential for molecular imaging based on the Xe biosensor in combination with HYPER-CEST. If the same images were acquired with the use of a conventional direct-detection methodology, over 870 hours would be required (Materials and Methods). Therefore, this technique marks a critical step toward the application of xenon biosensors as a selective contrast agent in biomedical MRI. Because the specificity of the sensor is determined by the functionality of its targeting agent, we envision that the combination of HYPER-CEST with the xenon biosensor can be used to image any molecular target for which an affinity agent (e.g., ligand or antibody) is known. Sensitivity relies predominantly on the S/N of the resonance of free Xe and is independent of the biosensor signal linewidth that previously limited the S/N (*8*). Moreover, this technique provides an adjustable contrast that can be switched on and off at will, because the HYPER-CEST effect depends on the saturation power [of course, the signal contrast as given in Fig. 2B also depends on the biosensor concentration (Materials and Methods)]. At this stage, we can detect a voxel of 22.5 μl ≈ $(2.8\ mm)^3$ in a coil volume of circa (ca.) 2.8 ml for a biosensor concentration of 5 μM. However, several possibilities for improvement should lead to even further sensitivity enhancement. Using isotopically enriched ^{129}Xe will increase the S/N by a factor of ~4, and optimized polarization procedures (*15*) can increase the signal by another factor of 15. Hence, these straightforward optimizations decrease the limit of detection by 60-fold to ~85 nM of Xe biosensor. This limit can be further decreased by increasing the cage-to-target ratio via chemical means, by designing the probe constructs such that the target molecule binds more than one biosensor (avidin, for example, has a capacity of 4), or by constructing each biosensor from more than one cryptophane cage, for example through dendrimeric amplification (*16*). By using these means, the minimum concentration of the target structure should reach the low nM to high pM range for optimized in vitro experiments. Hence, application of HYPER-CEST to xenon biosen-

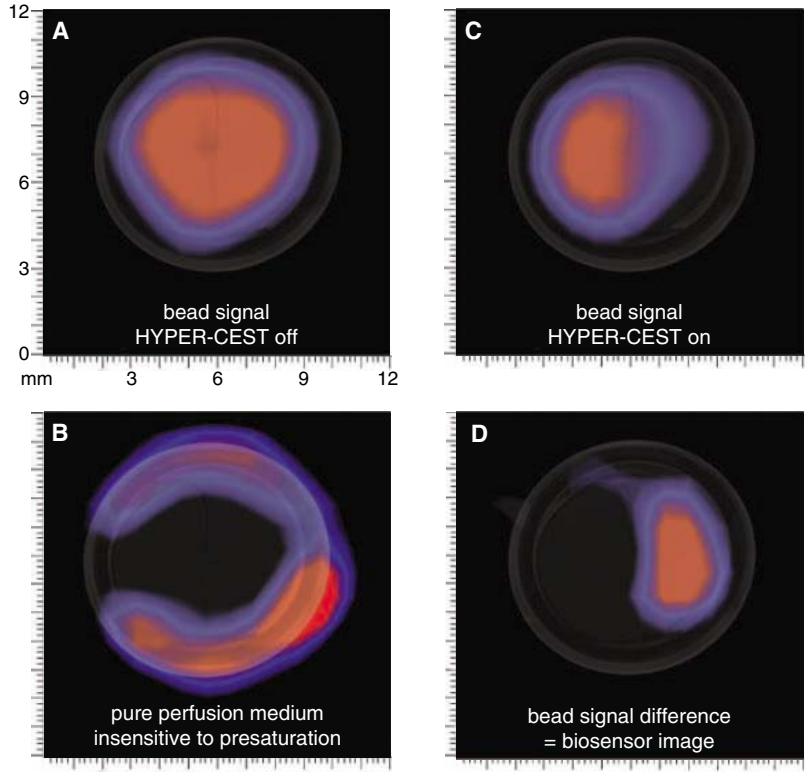

Fig. 3. Molecular imaging of the Xe biosensor (overlay of transverse ^{129}Xe images obtained from CSI data sets with the ^{1}H image shown in Fig. 2A). (**A**) Selective image for the bead signal at δ_1 and off-resonant cw saturation. (**B**) Selective image of the pure solution signal at δ_2. This signal corresponds to the surrounding outlet tube and is not affected by any saturation transfer. (**C**) On-resonant saturation of the biosensor resonance substantially depletes the δ_1 signal in volume 2. (**D**) The difference image of the two CSI data sets yields an exclusive mapping of compartment 2, i.e., a molecular image of the Xe biosensor.

sors represents an additional dimension of sensitivity and specificity for molecular imaging. The depletion process generating the image contrast depends on several parameters, including saturation power and time, sensor concentration, and ambient temperature. The latter parameter provides another promising approach to increase sensitivity even further, because the exchange rate increases considerably when approaching 37°C (*10*). Characterization of the saturation dynamics is currently under way and will reveal optimized parameters for future applications.

The technique is also quite promising for biomedical imaging in vivo. A typical surface coil of 20 cm diameter detects a volume of ca. 2.1 liters, thus decreasing S/N for a $(2.8\ mm)^3$ voxel by a factor of 27.2 compared with our setup. This loss is less than 50% of the gain for an optimized system using >45% polarized isotopically enriched ^{129}Xe. An isotropic resolution of 2 to 3 mm is feasible without signal averaging for a concentration of pure polarized ^{129}Xe that is ~2 μM in tissue. This minimum value is below those observed for direct injection of Xe-carrying lipid solutions into rat muscle (70 μM) or for inhalation delivery for brain tissue (8 μM) used in previous studies that demonstrated Xe tissue imaging in vivo (*17*). Sensitive molecular imaging of the biosensor is therefore possible as long as the distribution of dissolved xenon can be imaged with sufficient S/N and the biosensor target is not too dilute, because HYPER-CEST is based on the detection of the free Xe resonance, not direct detection of the biosensor resonance.

The HYPER-CEST technique is amenable to any type of MRI image acquisition methodology. We demonstrated CSI here, but faster acquisition techniques that incorporate a frequency encoding domain such as FLASH (fast low angle shot) have been successfully used to acquire in vivo Xe tissue images (*17*).

The modular setup of the biosensor (i.e., the nuclei that are detected are not covalently bound to the targeting molecule) allows accumulation of the biosensor in the tissue for minutes to hours before delivery of the hyperpolarized xenon nuclei, which have much higher diffusivity. In combination with the long spin-lattice relaxation time of Xe, this two-step process optimally preserves the hyperpolarization before signal acquisition. Biosensor cages that yield distinct xenon frequencies allow for multiplexing to detect simultaneously several different targets (*18*). Also the serum- and tissue-specific Xe NMR signals (*19*, *20*) arising after injection of the carrier medium can be used for perfusion studies (Fig. 3B) in living tissue, making Xe-CSI a multimodal imaging technique.

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21. This work was supported by the Director, Office of Science, Office of Basic Energy Sciences, Materials Sciences and Engineering Division, of the U.S. Department of Energy under contract no. DE-AC03-76SF00098. L.S. acknowledges support from the Deutsche Forschungsgemeinschaft (SCHR 995/1-1) through an Emmy Noether Fellowship. T.J.L. acknowledges the Graduate Research and Education in Adaptive bio-Technology (GREAT) Training Program of the UC Systemwide Biotechnology Research and Education Program (no. 2005-264), and C.H. acknowledges support from the Schweizerischer Nationalfonds through a postdoctoral fellowship.

Supporting Online Material

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Materials and Methods
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28 June 2006; accepted 29 August 2006
10.1126/science.1131847

Wetland Sedimentation from Hurricanes Katrina and Rita

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More than 131 × 10⁶ metric tons (MT) of inorganic sediments accumulated in coastal wetlands when Hurricanes Katrina and Rita crossed the Louisiana coast in 2005, plus another 281 × 10⁶ MT when accumulation was prorated for open water area. The annualized combined amount of inorganic sediments per hurricane equals (i) 12% of the Mississippi River's suspended load, (ii) 5.5 times the inorganic load delivered by overbank flooding before flood protection levees were constructed, and (iii) 227 times the amount introduced by a river diversion built for wetland restoration. The accumulation from hurricanes is sufficient to account for all the inorganic sediments in healthy saltmarsh wetlands.

Inorganic sediments accumulating in coastal wetlands may be delivered from inland sources via (i) unconstrained overbank flooding, (ii) explosive releases through unintentional breaks in constructed levees, and (iii) river diversions. They may also arrive from offshore during tidal inundation or storm events. It is important to know the quantities delivered by each pathway to understand how inorganic sediments contribute to wetland stability and to spend wetland restoration funds effectively. Here we estimate the amount of inorganic sediments deposited on wetlands of the microtidal Louisiana coast during Hurricanes Katrina and Rita.

Hurricanes Katrina and Rita passed through the Louisiana (LA) coast on 29 August and 24 September, 2005, respectively, leaving behind a devastated urban and rural landscape. Massive amounts of water, salt, and sediments were redistributed across the coastal zone within a few hours as a storm surge of up to 5 m propagated in a northerly direction at the coastline south of New Orleans, LA (Katrina), and near Sabine Pass, Texas (TX) (Rita), inundating coastal wetlands in the region. A thick deposit of mud remained in these coastal wetlands after the storm waters receded (Fig. 1). We used this post-storm remnant to learn about how coastal systems work.

The loss of LA's coastal wetlands peaked between 1955 and 1978 at 11,114 ha $year^{-1}$ (*1*) and declined to 2591 ha $year^{-1}$ from 1990 to 2000 (*2*). Coastal wetlands, barrier islands, and shallow waters are thought to provide some protection from hurricanes, by increasing resistance to storm surge propagation and by lowering hurricane storm surge height (*3*). Restoring LA's wetlands has become a political priority, in part because of this perceived wetland/storm surge connection. A major part of LA's restoration effort is to divert part of the Mississippi River into wetlands, and at considerable cost [ref. (*S1*) in supporting online material (SOM)]. Widely adopted assumptions supporting this

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diversion are that flood protection levees have eliminated overbank flooding, which has caused diminished sediment accumulation and eventual wetland loss, and introducing sediments into estuaries via river diversions will enhance wetland restoration.

If increasing inorganic sediment loading to coastal wetlands is important for their restoration, then it is important to quantify the major sediment pathways. Hurricanes Katrina and Rita obviously brought some inorganic sediment into the coastal wetlands, but how much, and where was it distributed? A few measurements of the inorganic sediments accumulating from a hurricane have been made at specific sites along the coast (*4*–*8*) [ref. (*S7*) in SOM], but until this study there were no coastwide data on the inorganic sediments accumulating from hurricanes. Here we show that the dominant pathway of inorganic sediments into the microtidal LA coastal wetlands is from offshore to inshore during hurricanes, and not from overbank flooding along the main channel of the Mississippi River, from smaller storm events, or from tidal inundations.

We sampled from the shoreline to the onshore limit of storm sediment deposition in wetlands (*9*) (Fig. 1A). We collected samples from all coastal watersheds in LA and at seven sites in eastern TX, using a helicopter and airboat (145 samples) or by walking out >20 m into the wetland from access points reached by boat or car (53 samples). Freshly deposited mud was easily identifiable from the layers beneath on the basis of color, texture, and density, and by the absence of plant debris (Fig. 1E). At least one preliminary sampling was done at each location (often three or four) before the final sample was taken. Samples for sediment depth (in centimeters) and density (in grams per cm^3) were taken only over the vegetation zone and not in rivulets between clumps of wetland plants.

The average bulk density of the newly deposited material was 0.37 g cm^{-3} (±1 SD = ± 0.35; range, 0 to 1.78 g cm^{-3}; n = 170 samples); it was highest near the coastline and decreased inland (Fig. 2B). The bulk density of material in these wetlands was determined by the amount of inorganic materials, not the organic content, and so bulk density multiplied by deposition height is an estimate of inorganic sediment deposition (*9*, *10*). Sediment with a bulk density >1 was largely composed of sand (Fig. 1A) (*9*). There was sparse plant debris (stems, leaves, and roots) in the newly deposited sediments within a few kilometers from the shoreline. The unconfirmed hypothesis is that the source materials from offshore came from where the bottom resistance to the hurricane winds before landfall was the greatest: in the shallow water zone immediately offshore of the deposition site.

The average dry weight accumulation of the deposition layer at all sampled locations was 2.23 g cm^{-2} (±1 SD = ± 3.4; range, 0 to 28.6 g cm^{-2}; n = 169) and 2.25 g cm^{-2} in the deltaic plain. The thickness of the newly deposited mud was 5.18 cm (±1 SD = ± 7.7; range, 0 to 68 g cm; n = 186). The thickest newly deposited sediments were observed inland of the area of maximum bulk density in eastern LA but were coincidental with the sediments of highest bulk density in western LA (Fig. 2C). The annualized average sediment accumulation from one hurricane was 89% of the average accumulation in healthy saltmarsh wetlands in the deltaic plain [0.166 g cm^{-2} $year^{-1}$ (*10*)].

Sediment deposition (in grams per cm^2) was greatest near the center of the storm track (Fig. 2D). The highest values in the Chenier Plain were on the east side of the hurricane path, where counterclockwise winds brought a storm surge inland, and were least on the western side, where water was withdrawn in a southerly direction out of the wetlands (Fig. 2, D to F). The greatest deposition in the Deltatic Plain was in the Breton Sound estuary, on the east side of the Mississippi River. The marshes within the 4° longitude distance between the two hurricanes (approximately 300 km) had intermediate rates of deposition. The peak water level, but not sediment accumulation, was higher in western Lake Pontchartrain during Hurricane Rita than during Hurricane Katrina because of these differences in wind fields (*11*). The peak in bulk density was highest on the eastern side of the center of the storm track.

There were peaks in sediment deposition where navigation channels confined the incoming storm surge to a narrow area at Sabine Pass, TX, and in the industrial canal by Paris Road, New Orleans, where the Intracoastal Waterway

Fig. 1. Examples of sediments deposited by Hurricanes Katrina and Rita. (**A**) Sand overwash on the former location of the coastal community of Holly Beach, LA (photo taken 18 November 2005 by R.E.T.). (**B**) Mud on the lawn of a St. Bernard Parish subdivision home (photo taken 27 September 2005 by M. Collins). (**C**) Mud on the marsh surface brought by Hurricanes Katrina and Rita (photo taken 16 November 2005 by J.B.). (**D**) Recent mud deposit (10.5 cm) accumulated over a root mass in the St. Bernard estuary (photo taken 16 November 2005 by J.B.). (**E**) Dried mud on the lawn of a Chalmette, LA, subdivision home, September 2005 (photo taken by R. Richards).

meets the Mississippi River Gulf Outlet. These observations are consistent with results from modeled storm surge velocities (*12*).

The total amount of recently deposited wetland sediments on the LA coast was calculated using information on the average sediment accretion and wetland area for each of four to six subunits of four coastal regions. The minimum amount of inorganic sediment brought in by these two hurricanes was estimated to be 131 × 10^6 metric tons (MT) (*9*) (Table 1). The average occurrence of a Category 3 or larger hurricane on this coast was every 7.88 years from 1879 to 2005 (*9*) (table S1). The annualized deposition from one hurricane would be 8.3 × 10^6 MT $year^{-1}$ if all hurricanes brought an equal amount of sediments to these wetlands. If sediments from these hurricanes are deposited in open-water areas at the same rate as in wetlands (*9*), then the pro rata deposition for open-water areas is proportional to the open water/wetland area (*1*) and is equal to 17.8 × 10^6 MT $year^{-1}$, for a combined sediment deposition of 26.1 × 10^6 MT $year^{-1}$.

The sediment accumulations in wetlands and open water were 4.0 and 8.5%, respectively, of the average annual suspended sediment load of the Mississippi River (210 × 10^6 MT $year^{-1}$) (Table 1) (*13*). The more frequent smaller storms not included in this analysis may also transport substantial amounts of inorganic material (*14*, *15*).

The amount of sediments delivered to coastal wetlands by Hurricanes Katrina and Rita was greater than the estimated amounts once flowing through or over Mississippi River banks. The suspended sediments overflowing unconfined (natural) levees of the Mississippi River in the past century were 4.8 × 10^6 MT $year^{-1}$, and 1.7 × 10^6 MT $year^{-1}$ in a confined levee system with occasional crevasses (Table 1). The Caernarvon Diversion, a restoration project located downstream from New Orleans, LA, delivered a 2-year average sediment load of 0.115 × 10^6 MT $year^{-1}$ (*16*). One conclusion to be drawn from these numbers is that the amount of sediment deposited on these wetlands from an average Category 3 or larger hurricane is 1.7 times the amount potentially available through unconfined overbank flooding, 4.6 times more than through crevasses in the unconfined channel, and 72 times more than from this river diversion. The combined sediment accumulation in wetlands and open water resulting from an average Category 3 or larger hurricane is 5.5 times larger than the material delivered by unconfined flow in the Mississippi River and 227 times larger than that delivered by the Caernarvon Diversion.

However, these comparisons are conservative estimates. Not all of the inorganic sediment flowing from rivers and over or through levees is deposited onto a wetland. Levees are higher than the surrounding land because inorganics settle out onto the levees or within the nearby marshes. Also, the peak in river heights, and hence in discharge, occurs in the spring when water levels in the estuary are at their seasonal low and wetlands are infrequently flooded (*17*). Sediments that do accumulate are deposited close to the diversion. For example, the Caernarvon Diversion distributes about 50% of its sediments into the wetlands for a maximum distance of about 6 km, covering about 15% of a direct path to the coastline (Table 1) (*18*). Hurricanes, in contrast, are much more democratic in that they flood the entire coastal landscape with new sediments.

A coastwide perspective on sediment loading to these wetlands, and perhaps to other microtidal coastal wetlands, is that most of the inorganics accumulating in them went down the Mississippi's birdfoot delta before they were deposited during large storms. The estimates indicate that the amount of storm-transported material is much greater than that introduced to wetlands from the historical overbank flow, from crevasses, or from river diversions. In particular, hurricanes appear to be the overwhelming pathway for depositing new inorganic sediments in coastal wetlands in western LA, because the few riverine sources bring relatively trivial amounts of inorganic sedi-

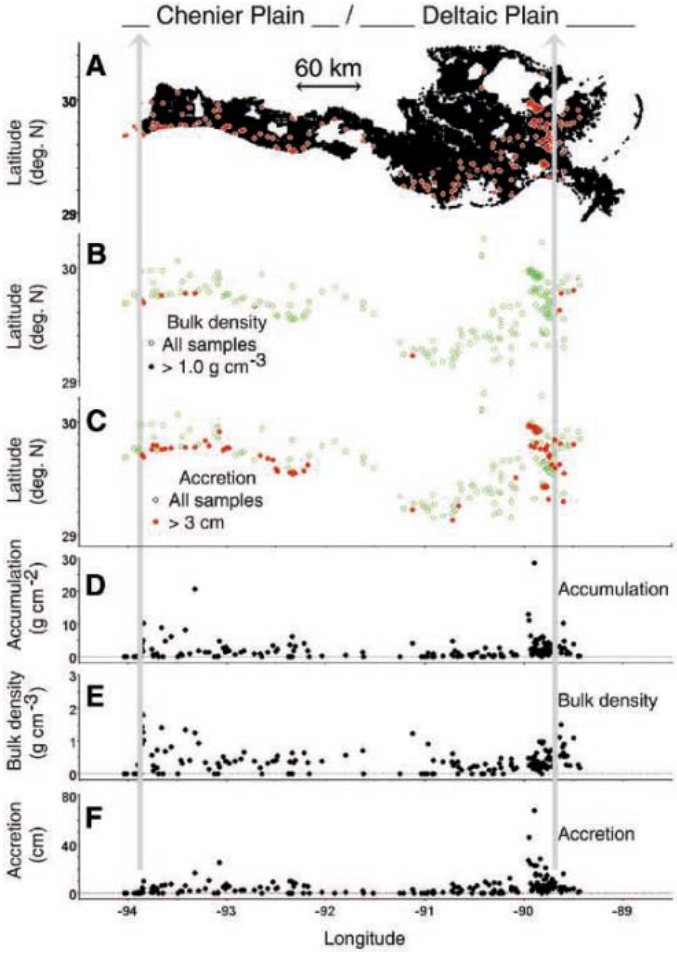

Fig. 2. Location of recent sediment samples and data arranged by longitude. (**A**) Sample locations (red dots) and the distribution of coastal wetlands in southern LA (black background). The vertical gray arrow is the crossing location of Hurricanes Rita (western LA) and Katrina (eastern LA). (**B**) All samples (open circles) and samples with a bulk density value >1.0 g cm^{-3} (red dots). (**C**) All samples (open circles) and samples with a vertical accretion >3 cm (red dots). (**D**) Accumulation relative to the longitude of sample collection (black circles). (**E**) Bulk density relative to the longitude of sample collection. (**F**) Vertical accretion relative to the longitude of sample collection.

Table 1. Estimates of the sediment source pathways for the Mississippi River deltaic plain in Louisiana.

Sediment source pathways	Amount (10^6 MT $year^{-1}$)
Mississippi River discharge into ocean (*13*)	210
One hurricane every 7.88 years (table S1)	
Onto wetland only	8.3
Onto wetland and into open water (*9*)	25.9
Overbank flooding (before flood protection levees) and into open water (*22*)	4.79
Crevasses through levees and into open water (*22*)	1.81
Caernarvon Diversion	
Into the estuary (*16*)	0.115
Onto wetland (*18*)	0.06

ments into the marsh. Because hurricanes are so important to the inorganic sediment budget, other factors must be considered to understand how to reduce wetland losses and further their restoration. Changes in the in situ accumulation of organics, rather than the reduction of inorganic sediments arriving via overbank flooding, are implicated as a causal agent of wetland losses on this coast. This is illustrated by the fact that the soil volume occupied by organic sediments plus water in healthy saltmarsh wetlands is >90% (*10*) and is certainly the same or higher in wetlands of lower salinity. This organic portion plays a major role in wetland soil stability and hence in wetland ecosystem health (*19*).

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23. Supported by the NSF Division of Geomorphology and Land-Use Dynamics (award EAR-061250), the National Oceanic and Atmospheric Administration Coastal Ocean Program MULTISTRESS (award no. NA16OP2670), and a Louisiana Board of Regents Fellowship (J.S.S.). We thank J. Gore for assistance in sampling from an airboat; E. Babin for assistance in finding photographs; H. Hampp, our deft, safe, and considerate helicopter pilot; and B. Sen Gupta, N. N. Rabalais, and three anonymous reviewers for constructive reviews of the manuscript.

Supporting Online Material

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Materials and Methods
SOM Text
Fig. S1
Table S1
References and Notes

24 April 2006; accepted 1 September 2006
Published online 21 September 2006;
10.1126/science.1129116
Include this information when citing this paper.

A Combined Mitigation/Geoengineering Approach to Climate Stabilization

T. M. L. Wigley

Projected anthropogenic warming and increases in CO_2 concentration present a twofold threat, both from climate changes and from CO_2 directly through increasing the acidity of the oceans. Future climate change may be reduced through mitigation (reductions in greenhouse gas emissions) or through geoengineering. Most geoengineering approaches, however, do not address the problem of increasing ocean acidity. A combined mitigation/geoengineering strategy could remove this deficiency. Here we consider the deliberate injection of sulfate aerosol precursors into the stratosphere. This action could substantially offset future warming and provide additional time to reduce human dependence on fossil fuels and stabilize CO_2 concentrations cost-effectively at an acceptable level.

In the absence of policies to reduce the magnitude of future climate change, the globe is expected to warm by ~1° to 6°C over the 21st century (*1*, *2*). Estimated CO_2 concentrations in 2100 lie in the range from 540 to 970 parts per million, which is sufficient to cause substantial increases in ocean acidity (*3*–*6*). Mitigation directed toward stabilizing CO_2 concentrations (*7*) addresses both problems but presents considerable economic and technological challenges (*8*, *9*). Geoengineering (*10*–*17*) could help reduce the future extent of climate change due to warming but does not address the problem of ocean acidity. Mitigation is therefore necessary, but geoengineering could provide additional time to address the economic and technological challenges faced by a mitigation-only approach.

The geoengineering strategy examined here is the injection of aerosol or aerosol precursors [such as sulfur dioxide (SO_2)] into the stratosphere to provide a negative forcing of the climate system and consequently offset part of the positive forcing due to increasing greenhouse gas concentrations (*18*). Volcanic eruptions provide ideal experiments that can be used to assess the effects of large anthropogenic emissions of SO_2 on stratospheric aerosols and climate. We know, for example, that the Mount Pinatubo eruption [June 1991 (*19*, *20*)] caused detectable short-term cooling (*19*–*21*) but did not seriously disrupt the climate system. Deliberately adding aerosols or aerosol precursors to the stratosphere, so that the loading is similar to the maximum loading from the Mount Pinatubo eruption, should therefore present minimal climate risks.

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Increased sulfate aerosol loading of the stratosphere may present other risks, such as through its influence on stratospheric ozone. This particular risk, however, is likely to be small. The effect of sulfate aerosols depends on the chlorine loading (*22*–*24*). With current elevated chlorine loadings, ozone loss would be enhanced. This result would delay the recovery of stratospheric ozone slightly but only until anthropogenic chlorine loadings returned to levels of the 1980s (which are expected to be reached by the late 2040s).

Figure 1 shows the projected effect of multiple sequential eruptions of Mount Pinatubo every year, every 2 years, and every 4 years. The Pinatubo eruption–associated forcing that was used had a peak annual mean value of –2.97 W/m² (*20*, *21*). The climate simulations were carried out using an upwelling-diffusion energy balance model [Model for the Assessment of Greenhouse gas–Induced Climate Change (MAGICC) (*2*, *25*, *26*)] with a chosen climate sensitivity of 3°C equilibrium warming for a CO_2 doubling ($2 \times CO_2$). Figure 1 suggests that a sustained stratospheric forcing of ~–3 W/m² (the average asymptotic forcing for the biennial eruption case) would be sufficient to offset much of the anthropogenic warming expected over the next century. Figure 1 also shows how rapidly the aerosol-induced cooling disappears once the injection of material into the stratosphere stops, as might become necessary should unexpected environmental damages arise.

Three cases are considered to illustrate possible options for the timing and duration of aerosol injections. In each case, the loading of the stratosphere begins in 2010 and increases linearly to

–3 W/m^2 over 30 years. The options depart from each other after this date (Fig. 2). These geoengineering options are complemented by three future CO_2 emissions scenarios: a central "no climate policy" scenario from the Special Report on Emissions Scenarios (SRES) (*27*) data set, namely the A1B scenario; an ambitious scenario known as WRE450 (*7*) in which CO_2 concentration stabilizes at 450 ppm (the present level is ~380 ppm); and an overshoot scenario in which CO_2 concentration rises to 530 ppm in 2080 before declining to 450 ppm. [Because an atmospheric CO_2 concentration of 450 ppm "produces both calcite and aragonite undersaturation in most of the deep ocean" (*4*), a level even less than this may ultimately be desirable.]

CO_2 concentrations and corresponding fossil fuel emissions for these three CO_2 scenarios are shown in Fig. 3. Emissions for the stabilization cases were calculated with the use of an inverse version of MAGICC, which accounted for climate feedbacks on the carbon cycle. The WRE450 scenario is an archetypal mitigation-only case, stabilizing at a level that many researchers believe would avoid "dangerous anthropogenic interference" with the climate system (*28*). The overshoot scenario is introduced here to be considered in conjunction with the three geoengineering options. It allows much larger CO_2 emissions and a much slower departure from the A1B no-policy scenario baseline. Although the rate of decline of emissions in the mid- to late 21st century is more rapid in the overshoot scenario than in WRE450, these reductions begin 15 to 20 years later in the former scenario, allowing additional time both to phase out existing CO_2-emitting fossil fuel energy technologies and to develop and deploy energy sources that have net-zero CO_2 emissions (*7*–*9*).

Figure 4 shows global mean temperature and sea-level projections for the no-policy scenario (A1B), the mitigation-only scenario (WRE450), and the overshoot CO_2 scenario combined with the three alternative geoengineering options (HIGH GEO, MID GEO, and LOW GEO). For the decades immediately after 2010, changes in aerosol forcing in all three GEO options occur more rapidly than forcing changes for the CO_2 scenarios, so the net effect is cooling. After 2040, the HIGH GEO–associated cooling tends to balance the warming from the overshoot CO_2 stabilization scenario, eventually leading to a slight cooling that would bring global mean temperatures back to near their preindustrial level. The MID and LOW GEO options lead to temperatures stabilizing at approximately 1° and 2°C relative to temperatures in 2000 (*29*). After 2100, the LOW GEO option (where injection into the stratosphere is decreased to zero by 2090) closely matches the WRE450 mitigation-only scenario but requires less-stringent emissions reductions.

The sea-level results (Fig. 4B), derived from models used in the Third Assessment Report

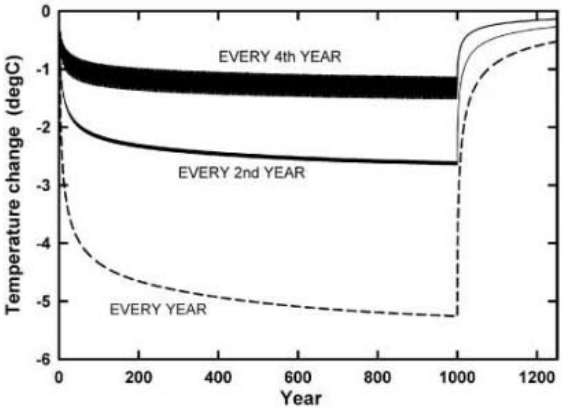

Fig. 1. (left) Global mean temperature response to multiple volcanic eruptions. The standard eruption used was that of Mount Pinatubo [forcing data from Ammann *et al.* (*20*, *21*)], and eruptions were assumed to occur every 4 years (top curve), every 2 years (middle curve), or every year (bottom curve). The results shown are annual mean values plotted year by year. In the 2- and (especially) 4-year cases, the forcing varies considerably from year to year, leading to noticeable interannual temperature variations. These appear as bands of values because the abscissa scale in the graph is insufficient to resolve these rapid variations. A climate sensitivity of 3°C equilibrium warming for 2 × CO_2 is assumed.

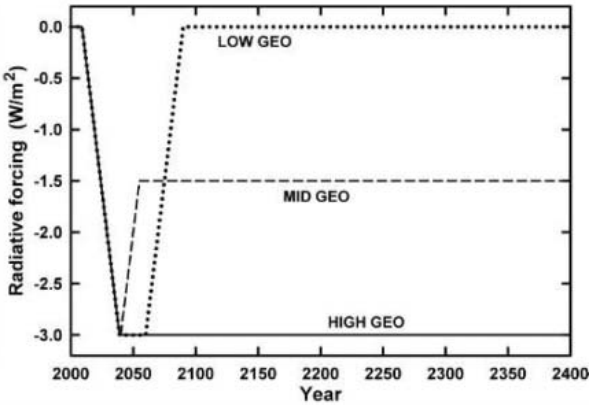

Fig. 2. (right) Radiative forcing scenarios for the three geoengineering options considered. The HIGH GEO option corresponds approximately to the steady-state forcing that would result from eruptions of Mount Pinatubo every 2 years.

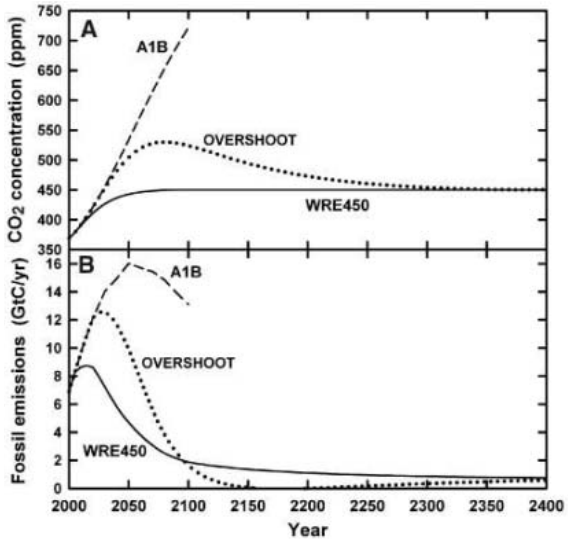

Fig. 3. (left) (**A**) CO_2 concentration projections used in the analysis together with (**B**) corresponding fossil fuel emissions. The overshoot scenario was used in conjunction with the three geoengineering options shown in Fig. 2. A climate sensitivity of 3°C equilibrium warming for 2 × CO_2 is assumed. CO_2 emissions results depend on the climate sensitivity because of climate feedbacks on the carbon cycle. GtC, gigatons of carbon.

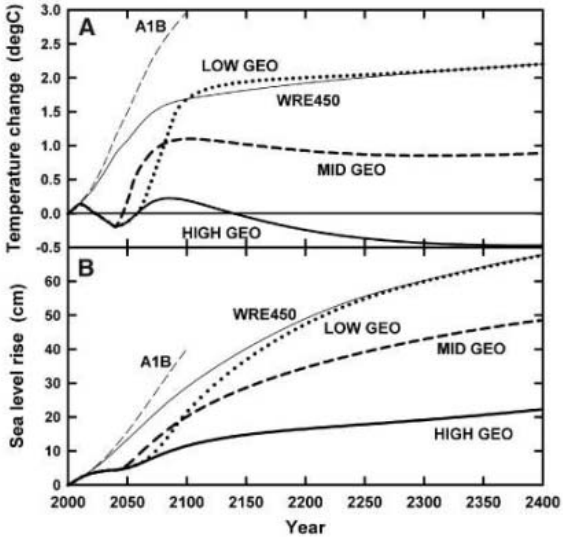

Fig. 4. (right) Global mean temperature (**A**) and sea-level (**B**) changes for the A1B scenario, the WRE450 scenario, and three scenarios combining both mitigation and geoengineering. The latter cases use the overshoot scenario (Fig. 3) and the three increasingly strong geoengineering options (Fig. 2). A climate sensitivity of 3°C equilibrium warming for 2 × CO_2 is assumed.

of the Intergovernmental Panel on Climate Change (*30*, *31*), show the much larger inertia of this part of the climate system. The LOW GEO option and WRE450 scenario again are similar, with neither tending toward stabilization. Even the HIGH GEO option shows a continuing (but slow) rise in sea level toward the end of the study period, but the rate of rise is small, even relative to changes observed over the 20th century (*30*, *32*).

A combined mitigation/geoengineering approach to climate stabilization has a number of advantages over either alternative used separately. A relatively modest geoengineering investment (*33*, *34*) corresponding to the present LOW GEO option could reduce the economic and technological burden on mitigation substantially, by deferring the need for immediate or near-future cuts in CO_2 emissions. More ambitious geoengineering, when combined with mitigation, could even lead to the stabilization of global mean temperature at near present levels and reduce future sea-level rise to a rate much less than that observed over the 20th century: aspects of future change that are virtually impossible to achieve through mitigation alone.

As a guide to the amount of SO_2 required, the eruption of Mount Pinatubo injected about 10 teragrams of sulfur (TgS) into the stratosphere (*35*, *36*), and the analysis here suggests that an annual flux of half that amount would have a substantial influence. Smaller diameter aerosols would have longer lifetimes and require still smaller injection rates (*15*). Five TgS/year is only ~7% of current SO_2 emissions from fossil fuel combustion (*37*, *38*). Further analysis is required to assess (i) the technological feasibility of the suggested injections of SO_2 [or of more radiatively efficient material (*34*)] into the stratosphere, (ii) the economic costs of this option relative to the reduced costs of mitigation that an overshoot CO_2–stabilization pathway would allow, and (iii) the detailed effects of the proposed SO_2 injections and CO_2 concentration changes on climate [compare with (*39*)] and stratospheric chemistry.

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40. The National Center for Atmospheric Research is supported by NSF.

26 June 2006; accepted 6 September 2006
Published online 14 September 2006;
10.1126/science.1131728
Include this information when citing this paper.

Dendritic Cell Stimulation by Mycobacterial Hsp70 Is Mediated Through CCR5

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An effective host immune response to mycobacterial infection must control pathogen dissemination without inducing immunopathology. Constitutive overexpression of mycobacterial heat shock protein (myHsp70) is associated with impaired bacterial persistence, but the immune-mediated mechanisms are unknown. We found that myHsp70, in addition to enhancing antigen delivery to human dendritic cells, signaled through the CCR5 chemokine receptor, promoting dendritic cell aggregation, immune synapse formation between dendritic cells and T cells, and the generation of effector immune responses. Thus, CCR5 acts as a pattern-recognition receptor for myHsp70, which may have implications for both the pathophysiology of tuberculosis and the use of myHsps in tumor-directed immunotherapy.

Mycobacterium tuberculosis infects one-third of the world's population and is responsible for two million deaths annually. A tightly controlled T cell response to *M. tuberculosis* results in granuloma formation, which limits mycobacterial replication and controls the immunopathological consequences of infection (*1*). The immune response and granuloma formation are regulated by host and mycobacterial factors (*2*); one of these, mycobacterial heat shock protein 70 (myHsp70), stimulates dendritic cells (DCs) to release proinflammatory mediators (*3*). Hsps are conserved between microorganisms and mammalian cells

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and have a well-characterized role in protein assembly (*4*). Their ability to bind and deliver short polypeptides to immature dendritic cells (iDCs) is being exploited in tumor-directed DC immunotherapy (*5*). Picomolar concentrations of peptide bound to myHsp70 can generate antigen-specific cytotoxic T lymphocyte (CTL) responses through efficient peptide delivery and direct iDC stimulation by myHsp70 (*6*). A calcium-dependent intracellular signaling cascade triggered by myHsp70, but not by Toll-like receptor (TLR) agonists (*6*), is critical for the generation of effector immune responses, but neither the surface receptor nor the cellular mechanisms involved are known.

To further characterize the myHsp70-mediated calcium signal in iDCs, we demonstrated that pertussis toxin, an inhibitor of heterotrimeric G-protein–coupled receptor (GPCR) transduction, inhibited signaling of both myHsp70 and the control GPCR-mediated agonist, N-formyl-Met-Leu-Phe (fMLP; Fig. 1A). Analysis of potential GPCRs expressed on iDCs, using a heterologous expression system, revealed that myHsp70 signaled through a CC chemokine receptor. We examined glioma cells expressing different chemokine receptors and found that myHsp70 triggered a calcium response in cells expressing CCR5, and to a much lesser extent CCR1 (Fig. 1B). Alexa488-conjugated myHsp70 showed specific binding to

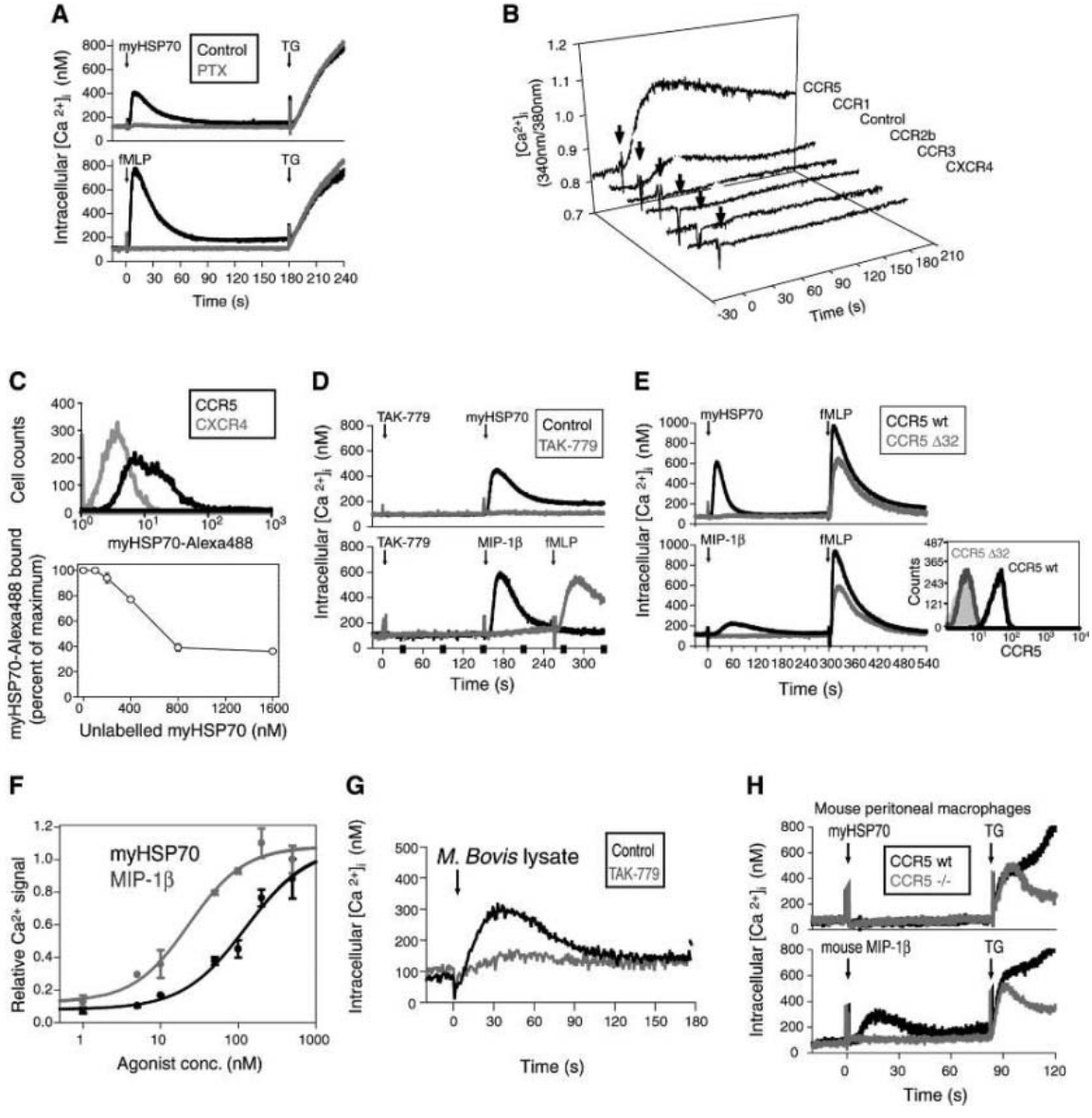

Fig. 1. myHsp70 triggers intracellular signaling in human iDCs through CCR5. (**A**) The myHsp70 receptor on human DCs is G-protein–coupled. Calcium signaling in iDCs, preincubated with (gray) or without (black) pertussis toxin (PTX, 1 μg/ml for 12 hours), after stimulation with myHsp70 (200 nM, top), fMLP (1 μM, bottom), or subsequently thapsigargin (TG, 1 μM) is shown. (**B**) Calcium signaling in chemokine receptor–expressing glioma cell lines after myHsp70 stimulation (200 nM, arrows). (**C**) myHsp70 binds to CCR5. (Top) Alexa488-labeled myHsp70 (220 nM) staining of CCR5-expressing (black) versus control CXCR4-expressing (gray) cells. (Bottom) Labeled myHsp70 (220 nM)–specific binding was inhibited by increasing doses of unlabeled myHsp70. (**D**) TAK779 inhibits myHsp70 calcium signaling. Calcium signaling in iDCs, pretreated with TAK-779 (100 nM, gray), or vehicle alone (black) after the addition of myHsp70 (200 nM, top), MIP-1β (100 nM), or fMLP (1 μM, bottom) is shown. (**E**) The CCR5Δ32 mutation confers resistance to myHsp70. Calcium responses in iDCs homozygous for wild-type (wt) CCR5 (black) or CCR5Δ32 (gray) after stimulation with myHsp70 (30 nM, top) or MIP-1β (200 nM, bottom), followed by fMLP (1μM), are shown. (Lower inset) CCR5 expression on CCR5 wild-type (black) or CCR5Δ32 (gray) iDCs (iDC isotype: gray fill). (**F**) Dose response of myHsp70 (black) versus MIP-1β (gray) calcium signaling in iDCs. (**G**) *M. bovis* lysates trigger calcium responses through CCR5 in iDCs. Calcium responses in untreated (black) or TAK-779–pretreated (gray) iDCs after treatment with *M. bovis* BCG lysate (arrow) are shown. (**H**) myHsp70 does not signal via murine CCR5. Calcium signaling in mouse peritoneal macrophages from $CCR5^{+/+}$ (black) and $CCR5^{-/-}$ (gray) mice after the addition of myHsp70 (top) or mouse MIP-1β (bottom) is shown.

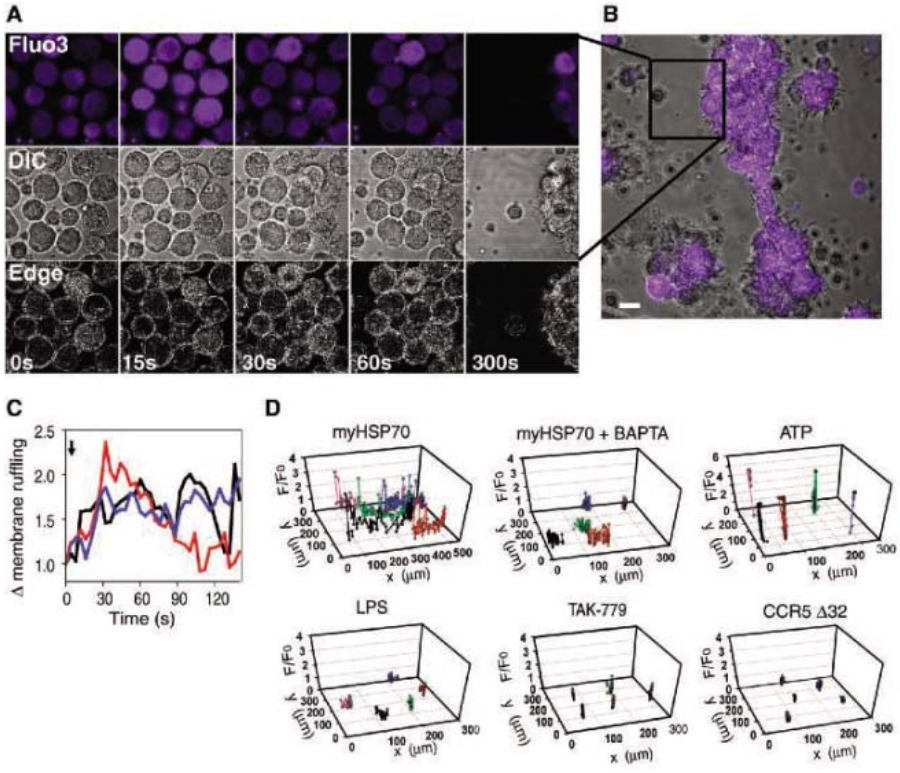

Fig. 2. myHsp70 signaling triggers rapid calcium-dependent iDC aggregation. (**A**) myHsp70 induces changes in iDC morphology and trafficking. Simultaneous fluorescence (top) and DIC (middle) (×100) imaging of Fluo3-labeled iDCs after the addition of myHsp70 (200 nM) is shown. DIC images were analyzed with edge-detection analysis software (bottom) to enhance the visualization of membrane ruffling. (**B**) Merged fluorescence and DIC images from the experiment shown in (A) 450 s after the addition of myHsp70, at lower (×40) magnification. (**C**) Quantification of membrane ruffling after myHsp70 addition. The fold increase in the edge signal derived from image analysis is shown for three representative cells. The arrow indicates addition of myHsp70. (**D**) myHsp70 calcium responses are required for iDC aggregation. The correlation of intracellular calcium concentration (F/F_0) with cell movement [determined by *x*-*y* displacement (analyzed every 5 s)] in iDCs treated with myHsp70 (200 nM), myHsp70 after preincubation with the intracellular calcium chelator BAPTA-AM, ATP (100 μM), LPS (100 ng/ml), TAK-779 (1 μM), or iDCs from CCR5Δ32 homozygotes treated with myHsp70 is shown.

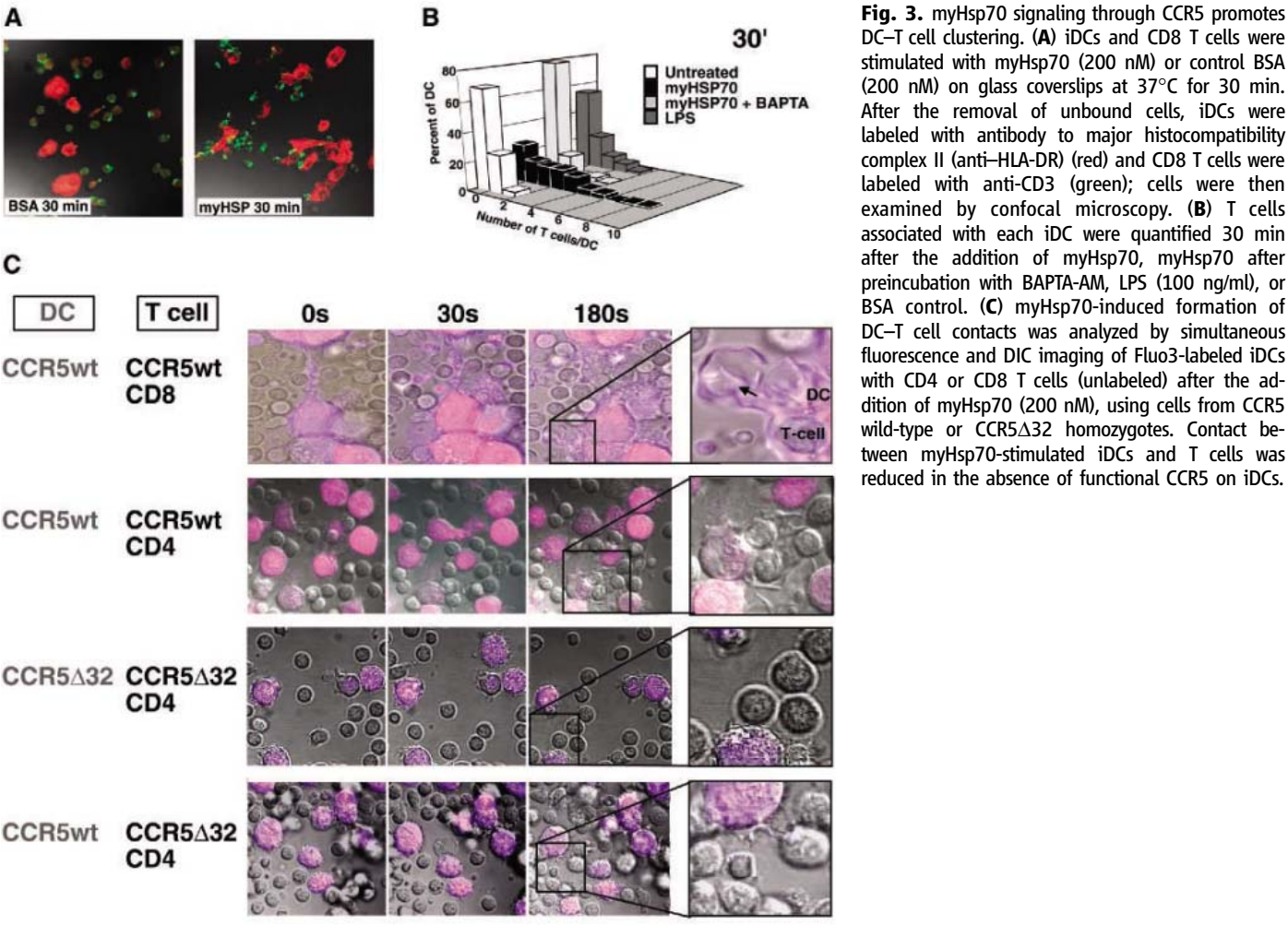

Fig. 3. myHsp70 signaling through CCR5 promotes DC–T cell clustering. (**A**) iDCs and CD8 T cells were stimulated with myHsp70 (200 nM) or control BSA (200 nM) on glass coverslips at 37°C for 30 min. After the removal of unbound cells, iDCs were labeled with antibody to major histocompatibility complex II (anti–HLA-DR) (red) and CD8 T cells were labeled with anti-CD3 (green); cells were then examined by confocal microscopy. (**B**) T cells associated with each iDC were quantified 30 min after the addition of myHsp70, myHsp70 after preincubation with BAPTA-AM, LPS (100 ng/ml), or BSA control. (**C**) myHsp70-induced formation of DC–T cell contacts was analyzed by simultaneous fluorescence and DIC imaging of Fluo3-labeled iDCs with CD4 or CD8 T cells (unlabeled) after the addition of myHsp70 (200 nM), using cells from CCR5 wild-type or CCR5Δ32 homozygotes. Contact between myHsp70-stimulated iDCs and T cells was reduced in the absence of functional CCR5 on iDCs.

CCR5-expressing but not control CXCR4-expressing cells (Fig. 1C) and was inhibited by competition with unlabeled myHsp70 (Fig. 1C). CCR5-dependent signaling also occurred in primary human DCs, because the CCR5 antagonist TAK-779 (*7*) inhibited calcium signaling in iDCs triggered by myHsp70 and the endogenous CCR5 ligand, MIP-1β, but not calcium signaling by fMLP (Fig. 1D).

The requirement for CCR5 in myHsp70 signaling was confirmed by examining calcium responses in iDCs from a donor homozygous for the CCR5Δ32 allele, the naturally occurring 32-nucleotide deletion that prevents CCR5 surface expression (*8*) (Fig. 1E and fig. S1). The absence of myHsp70- or MIP-1β–mediated calcium signaling in CCR5Δ32 iDCs confirmed an absolute requirement for CCR5 in this pathway (Fig. 1E). A dose-response comparison of calcium signals in iDCs showed MIP-1β to be five times more potent than myHsp70 (Fig. 1F). A lysate from *M. bovis* bacille Calmette Guérin (BCG) also triggered a TAK-779–inhibitable calcium signal, suggesting that sufficient myHsp70 is present to promote CCR5-dependent signaling (Fig. 1G). Furthermore, CCR5-dependent myHsp70 signaling was species-specific, because no myHsp70 signal was seen in CCR5-expressing mouse macrophages (Fig. 1H), myHsp70 did not involve TLR signaling pathways [as assessed by microarray analysis (fig. S2A and table S1) and assays of nuclear factor κB activity (fig. S2, B and C)], and myHsp70 induces a calcium-dependent phenotypic maturation of DCs (fig. S3).

The immediate morphological consequences of CCR5-mediated Hsp70 calcium signaling were further investigated by live cell imaging of iDCs (Fig. 2, A to C, and video S1). The addition of myHsp70 triggered calcium oscillations, immediately followed by rapid cell membrane ruffling and pseudopodia projection (Fig. 2C). Correlation of intracellular calcium oscillations with cell movement, by means of simultaneous fluorescence differential interference contrast (DIC) imaging, suggested that a rise in intracellular calcium was required, but not sufficient, to trigger membrane changes and cell aggregation. Membrane changes and cell aggregation were inhibited by chelation of intracellular calcium and could not be induced by calcium rises induced by adenosine triphosphate (ATP) or phorbol myristate acetate/ionomycin (Fig. 2D and fig. S4). These morphological changes were also mediated through CCR5. They were inhibited by TAK-779, were not seen in DCs from CCR5Δ32 homozygotes (Fig. 2D), and were not induced by TLR agonists (Fig. 2D). Thus, myHsp70 stimulation of human DCs results in rapid CCR5-mediated, calcium-dependent, nonrandom migration of iDCs and the projection of plasma membrane extensions.

To examine how myHsp70 affected interactions between DCs and T cells, we stimulated iDCs and autologous T cells with myHsp70. Autologous T cells rapidly clustered around the DCs (Fig. 3A). More T cells (up to nine) associated with each DC after stimulation with myHsp70 than with bovine serum albumin (BSA) or lipopolysaccharide (LPS), and this enhanced interaction was inhibited by 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA) preloading (Fig. 3B). The trapping of T cells by DCs was observed as early as 30 s after stimulation of iDCs (Fig. 3C and videos S2 and S3), was facilitated by the formation of a network of DC membrane extensions (Fig. 3C), and was seen with both autologous and allogeneic CD4 and CD8 T cells (Fig. 3C). The formation of the membrane extensions and T cell clusters was dependent on functional CCR5 receptors on DCs but not on T cells (Fig. 3C and video S4). The rapid clustering of DCs and associated T cells suggested an integrin-mediated mechanism. The addition of myHsp70 led to a rapid increase in β_2-integrin–specific iDC binding to immobilized intercellular adhesion molecule–2 (ICAM-2), ICAM-3, and (to a lesser extent) ICAM-1 (Fig. 4A) (*9*). This rapid T cell trapping by DCs stimulated with myHsp70 was followed at later time points (after 30 min) by T cell polarization of talin and LFA-1 toward the point of contact with the DC (Fig. 4B), suggesting the formation of antigen-independent immune synapses (*10*, *11*). The ability of myHsp70 to promote iDC–T cell interactions may explain why T cells are required for myHsp70 to stimulate pro-inflammatory cytokine release from DCs (fig. S5) (*6*).

CCR5 mediated a number of functional consequences of myHsp70 signaling. myHsp70 and

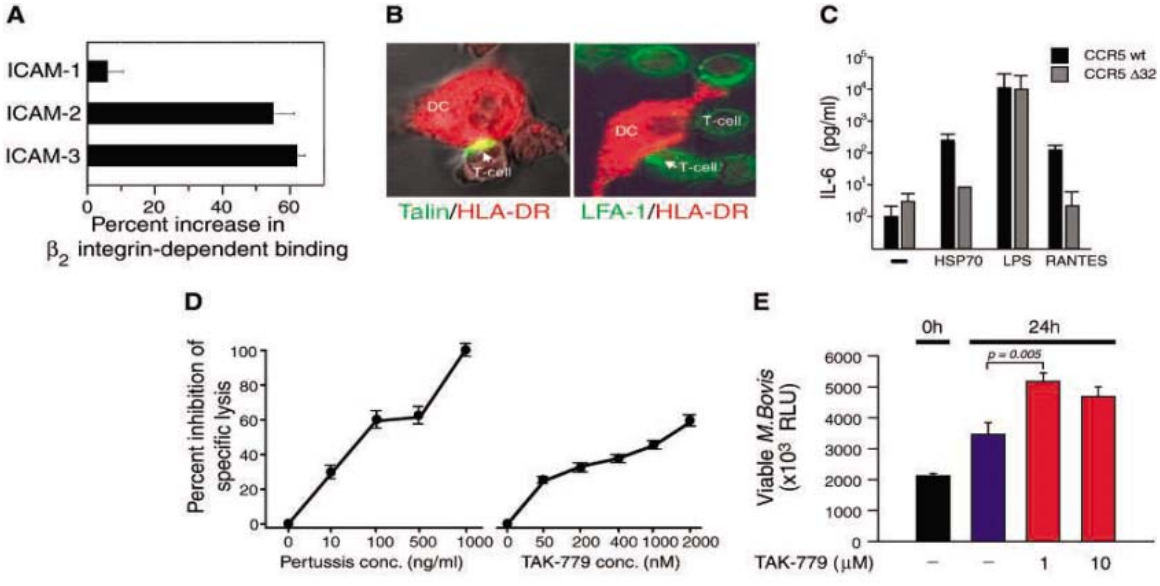

Fig. 4. myHsp70 signaling through CCR5 promotes functional DC–T cell immune synapse formation. (**A**) myHsp70 up-regulates β_2 integrin activity. β_2-integrin–dependent adherence of iDCs to substrate coated with ICAM-1, -2, or -3 measured 10 min after treatment with myHsp70 or vehicle is shown. (**B**) myHsp70 induces DC–T cell immune synapse formation. Thirty minutes after stimulation with myHsp70 (200 nM), T cells (green) and iDCs [labeled with anti–HLA-DR (red)] were examined for polarization of talin (left) and LFA-1 (right) by confocal microscopy. (**C**) CCR5Δ32 iDCs show impaired IL-6 release after myHsp70 treatment. IL-6 release from CCR5 wild-type (black bars) or CCR5Δ32 (gray bars) iDCs 72 hours after stimulation with myHsp70 (200 nM), LPS (0.5 ug/ml), or RANTES (400 nM) is shown. (**D**) TAK-779 and pertussis toxin block the generation of peptide-specific CTLs by myHsp70. myHsp70-peptide–pulsed iDCs were used to generate antigen-specific CTLs (*6*). The effect of pretreating iDCs with increasing concentrations of pertussis toxin (left) or TAK-779 (right) on the induction of peptide-specific CTLs by Hsp70 was determined. Results are shown as percent inhibition of specific lysis, where inhibition is plotted as a percentage of the maximal response ($n = 3$ replicates ± SEM). (**E**) The effect of TAK-779 on intracellular mycobacteria replication. iDCs from immune individuals were incubated for 2 hours with *M. bovis* BCG-lux, washed to remove noninternalized mycobacteria, and cocultured with autologous $CD4^+$ and $CD8^+$ T cells in the absence (blue) or presence (red) of TAK-779. Cell-associated luminescence (correlating with viable mycobacteria) was determined in triplicate samples before and 24 hours after the addition of T cells. Results are representative of three separate experiments.

the CCR5 agonist RANTES induced interleukin-6 (IL-6) release from wild-type but not CCR5Δ32 iDCs (Fig. 4C). Furthermore, pretreatment of iDCs with pertussis toxin or TAK-779 inhibited the ability of peptide-loaded myHsp70 to stimulate DCs to generate influenza peptide–specific CTLs (Fig. 4D). To examine the effect of CCR5-mediated signaling in mycobacterial infection, we used the model pathogen *M. bovis* BCG-lux (*12*). As reported for murine DCs (*13*), human DCs from immune people were unable to kill internalized mycobacteria, even in the presence of autologous T cells. TAK-779 inhibition of CCR5 led to a dose-dependent enhancement of intracellular mycobacterial replication (Fig. 4E and fig. S6A) at all concentrations of mycobacteria tested (fig. S6B), suggesting an important role for this receptor in controlling mycobacterial infection.

The identification of CCR5 as the critical receptor for myHsp70-mediated DC stimulation has implications for both mycobacterial infection and the therapeutic use of myHsp70. CCR5 is important in immune cell cross talk. Interaction with its naturally occurring ligand MIP-1β promotes the recruitment of cells to sites of inflammation (*14*), facilitates immune synapse formation (*15*), orchestrates T cell interactions within lymph nodes (*16*), and controls the activation and differentiation of T cells (*17*). Our finding that a mycobacterial lysate, as well as purified myHsp70, stimulated a CCR5-dependent calcium response indicates a further connection between the innate and adaptive immune responses during mycobacterial infection. The cellular aggregation induced by myHsp70 signaling through CCR5 may play an important role in the formation of granulomas, the hallmark of mycobacterial infection.

Microbial-induced DC responses need to be highly regulated, reflecting a balance between a rapid and appropriate response to invading microbes and the inducement of immunopathology (*2*)—a particular problem in mycobacterial infection. An increasing number of human pathogens, including HIV (*18*), toxoplasma (*19*), and *M. tuberculosis* (as described here), target the CCR5 receptor. This role of CCR5 as a pattern-recognition receptor for myHsp70 may, at least in part, be responsible for the maintenance of the high CCR5Δ32 allele frequency (10 to 15%) in Northern European populations (*20*) and may alter the pattern of disease seen in people with the CCR5Δ32 allele.

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21. We are grateful to M. Mahaut-Smith for the use of the Cairn Spectrophotometer and A. Betz for CCR5$^{-/-}$ mice. Funded by the Wellcome Trust (P.J.L.), the Medical Research Council (R.A.F.), the Swiss National Science Foundation (J.P.), and FEBS (E.H.). P.J.L. holds a Lister Institute Research Prize.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5798/454/DC1
Materials and Methods
Figs. S1 to S7
Table S1
Videos S1 to S4
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26 May 2006; accepted 8 September 2006
10.1126/science.1133515

Direct Demonstration of an Adaptive Constraint

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The role of constraint in adaptive evolution is an open question. Directed evolution of an engineered β-isopropylmalate dehydrogenase (IMDH), with coenzyme specificity switched from nicotinamide adenine dinucleotide (NAD) to nicotinamide adenine dinucleotide phosphate (NADP), always produces mutants with lower affinities for NADP. This result is the correlated response to selection for relief from inhibition by NADPH (the reduced form of NADP) expected of an adaptive landscape subject to three enzymatic constraints: an upper limit to the rate of maximum turnover (k_{cat}), a correlation in NADP and NADPH affinities, and a trade-off between NAD and NADP usage. Two additional constraints, high intracellular NADPH abundance and the cost of compensatory protein synthesis, have ensured the conserved use of NAD by IMDH throughout evolution. Our results show that selective mechanisms and evolutionary constraints are to be understood in terms of underlying adaptive landscapes.

The old notion of natural selection as an omnipotent force in biological evolution has given way to one where adaptive processes are constrained by physical, chemical, and biological exigencies (*1*–*4*). Whether constraint and/or stabilizing selection explain phenotypic stasis, in the fossil record and in phylogenies, remains an open question (*5*). Direct experimental tests of constraint are scarce (*6*–*9*). Even tight correlations among traits, at once suggestive of constraint, can be broken by artificial selection to produce new phenotypic combinations (*8*, *9*). Despite all circumstantial evidence, results from direct experimental tests imply that selection is largely unconstrained.

The direct experimental test for constraint is conceptually simple. A phenotype is subjected to selection (natural or artificial) in an attempt to break the postulated constraint (*6*–*9*). A response to selection indicates a lack of constraint. No response to selection indicates the presence of a constraint. However, the cause of a constraint is rarely specified because the etiologies of most phenotypes are not well understood, their relationships to fitness are usually opaque, and a lack of response to selection may reflect nothing more than a lack of heritable variation (*4*, *7*). If the cause of a constraint is to be elucidated, it must be for a simple phenotype whose relationship to fitness is understood.

Coenzyme use by β-isopropylmalate dehydrogenase (IMDH) is a simple phenotype whose etiology and relationship to fitness are understood (*10*, *11*). IMDHs catalyze the oxidative decarboxylation of β-isopropylmalate to α-ketoisocaproate during the biosynthesis of leucine, an essential amino acid. All IMDHs use nicotinamide adenine dinucleotide (NAD) as a coenzyme (cosubstrate). This invariance of function among IMDHs hints at the presence of ancient constraints, even though some related isocitrate dehydrogenases (IDHs) use NADP instead (*12*, *13*).

Structural comparisons with related NADP-using IDHs identify amino acids controlling coenzyme use (*14*–*16*) (Fig. 1A). Introducing five replacements (Asp^{236} → Arg, Asp^{289} → Lys, Ile^{290} → Tyr, Ala^{296} → Val, and Gly^{337} → Tyr) into the coenzyme-binding pocket of *Escherichia coli leuB*–encoded IMDH by site-directed mutagenesis causes a complete reversal in specificity (*10*, *11*): NAD performance (k_{cat}^{NAD}/K_m^{NAD}, where K_m is the Michaelis constant) is reduced by a factor of 340, from 68×10^3 M^{-1} s^{-1} to 0.2×10^3 M^{-1} s^{-1}, whereas NADP performance ($k_{cat}^{NADP}/K_m^{NADP}$) is increased by a factor of 70, from 0.49×10^3 M^{-1} s^{-1} to 34×10^3 M^{-1} s^{-1}. The engineered LeuB[RKYVYR] mutant (the final R represents Arg^{341}, already present in wild-type *E. coli* IMDH) is as active and as specific toward NADP as the wild-type enzyme is

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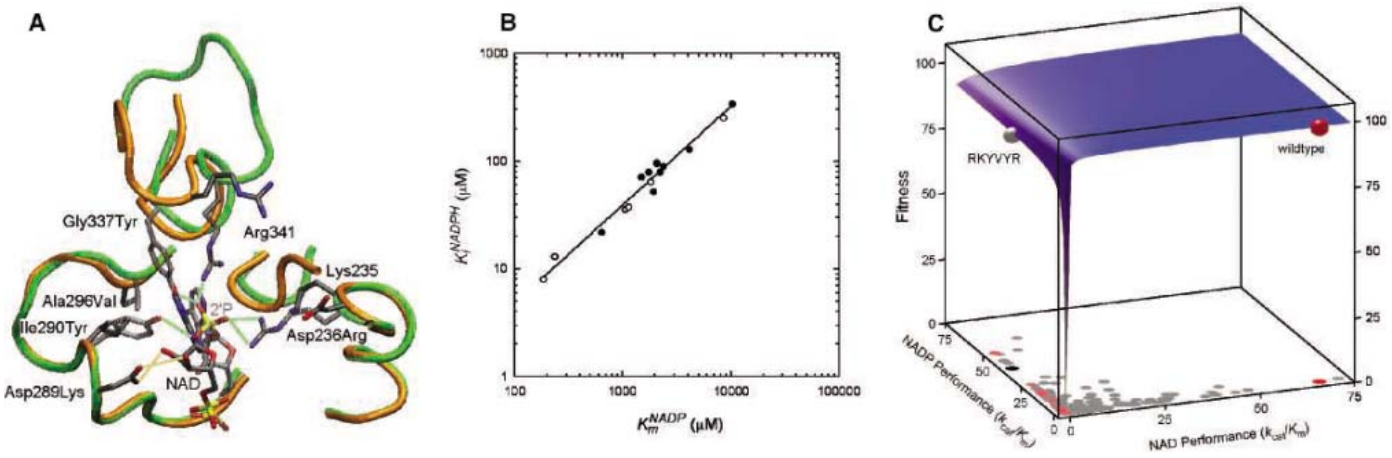

Fig. 1. The molecular anatomy of an adaptive constraint. (**A**) Structural alignment of the coenzyme binding pockets of *E. coli* IMDH (*14*) (brown main chain) with bound NAD modeled from *Thermus thermophilus* IMDH (*15*) and *E. coli* IDH (*16*) (green main chain) with bound NADP. Only key residues are shown (gray, carbon; red, oxygen; blue, nitrogen; yellow, phosphorus) with labels designating the amino acid and site number in IMDH followed by the amino acid in IDH. Coenzyme use is determined by H bonds to NAD (brown lines) and to the 2′-phosphate (2′P) of NADP (green lines). (**B**) Mutations in the coenzyme binding pocket that stabilize NADP also stabilize NADPH. The ensuing correlation in affinities for NADP (K_m^{NADP}) and NADPH (K_i^{NADPH}) seen with engineered mutants (circles) (*11*) is retained in the screened mutants (dots). (**C**) The adaptive landscape for coenzyme use by IMDH (*11*) showing the phenotype-fitness map (blue surface) determined in chemostat competition and described by equation S5 (*11*, *18*) and the predicted distribution of performances for 512 mutants in the coenzyme binding pocket (gray dots), with wild type (red dot), LeuB[RKYVYR] (black dot), and single amino acid replacements in LeuB[RKYVYR] coenzyme binding pocket (pink dots). The fitness of LeuB[RKYVYR] is hypothesized to be lower than in the wild type because of strong inhibition by abundant intracellular NADPH (*11*).

toward NAD. Evidently, protein architecture has not constrained IMDH to use NAD since the last common ancestor.

Despite similar in vitro performances, the NADP-specific LeuB[RKYVYR] mutant is less fit than the NAD-specific wild type (*11*). IMDHs, wild-type and mutant alike, display a factor of 30 higher affinity for the reduced form of NADP (NADPH) (coproduct) than for NADP (Fig. 1B). We suggested the LeuB[RKYVYR] mutant is subject to intense inhibition by intracellular NADPH, which is far more abundant in vivo than is NADP (*11*, *17*). The inhibition slows leucine biosynthesis, reduces growth rate, and lowers Darwinian fitness (Fig. 1C). The wild type retains high fitness because its affinity for NADPH is low, whereas inhibition by NADH, which is far less abundant than NAD in vivo, is ineffective. Perhaps as a consequence of differences in Michaelis complex structure (*18*), IDH is not subject to such intense NADPH inhibition and hence could evolve NADP use.

We hypothesize that IMDH is constrained to use NAD because the strong inhibition associated with NADP use reduces fitness. However, identifying the mechanism of selection (NADPH inhibition) is not synonymous with identifying the causes of constraint. Mutations that increase k_{cat}^{NADP} (maximum rate of NADP turnover), that break the correlation in NADP and NADPH affinities (Fig. 1B), or that eliminate the trade-off in coenzyme performances (Fig. 1C) could each benefit the LeuB[RKYVYR] mutant without compromising its performance with NADP (*18*). We therefore hypothesize that IMDH is constrained to use NAD by three causes: an upper limit to k_{cat}^{NADP}, an unbreakable correlation in the affinities of NADP and NADPH, and an inescapable trade-off in coenzyme performance.

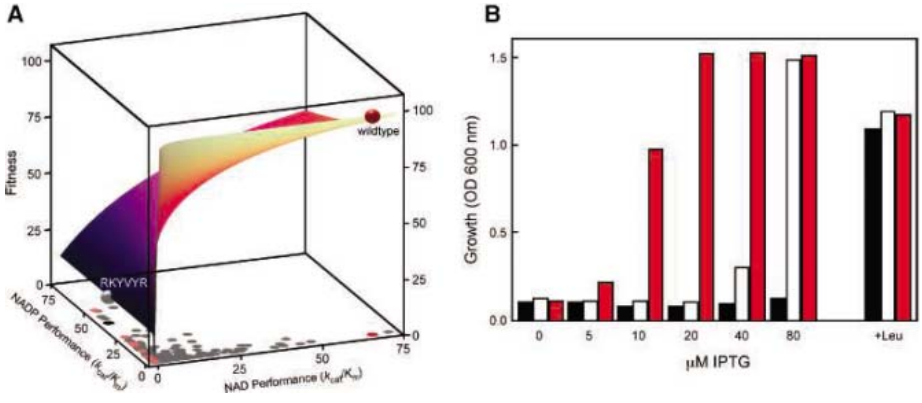

Fig. 2. The phenotypic basis of the genetic screen. Lowered expression in the presence of excess glucose brings IMDH to saturation with isopropylmalate, increasing coenzyme affinities. (**A**) Lowering IMDH expression in the chemostat-derived adaptive landscape [lower concentration of *E* in equation S5 (*11*, *18*)] is predicted to reduce the fitness of LeuB[RKYVYR] (white sphere) far more than that of the wild type (red sphere). (**B**) IPTG-controlled expression of IMDHs ligated downstream of the T7 promoter in pETcoco in strain RFS[DE3] (*leuA*$^+$*B*^{am}*C*$^+$, with T7 RNA polymerase expressed from a chromosomal *lacUV5* promoter) confirms that lower expression affects growth in minimal glucose medium of the LeuB[RKYVYR] (white) more than in the wild type (red). Plasmids lacking LeuB (black) are incapable of growth except in the presence of leucine.

We used directed evolution (targeted random mutagenesis and selective screening) (*19*–*21*) to test whether NADP-specific IMDHs with higher fitness could be isolated. Random substitutions were introduced into *leuB[RKYVYR]* by means of error-prone polymerase chain reaction (*18*). Mutated alleles were ligated downstream of the T7 promoter in pETcoco (a stable single-copy vector) and transformed into strain RFS[DE3] (*leuA*$^+$*B*^{am}*C*$^+$, with T7 RNA polymerase expressed from a chromosomal *lacUV5* promoter). Sequencing unscreened plasmids revealed that, on average, each 1110–base pair *leuB[RKYVYR]* received two nucleotide substitutions. From the pattern of base substitutions in these mutants and assuming Poisson statistics, we estimate that only 10.5 (0.4%) of the 2431 possible amino acid replacements were missing in our mutant library (*18*).

Our experimental design used decreased IMDH expression to provide a simple selective screen for mutations in *leuB[RKYVYR]* that increase growth and/or fitness. As predicted from the phenotype-fitness map (Fig. 2A), selection against *leuB[RKYVYR]* intensified as IMDH expression was lowered in the presence of excess glucose (Fig. 2B). Using 40 μM isopropyl-β-D-thiogalactopyranoside (IPTG) to induce a low level of IMDH expression, we found that cells harboring *leuB[WT]* formed large colonies at 24 hours, whereas cells harboring *leuB[RKYVYR]*

barely formed pinprick colonies at 48 hours. We chose colony formation at 48 hours as the least stringent criterion compatible with reliably identifying beneficial mutations in *leuB[RKYVYR]*. Longer periods of growth (or higher concentrations of IPTG) allowed unmutated *leuB[RKYVYR]* to form colonies, whereas shorter periods (or lower concentrations of IPTG) produced no colonies.

Of the 100,000 mutated plasmids screened, 134 (representing 107 distinct isolates) formed colonies within 48 hours (table S1). Each had either a substitution in the 5′ leader sequence upstream of *leuB[RKYVYR]*, an amino acid replacement in the coenzyme binding pocket, or both. Upstream substitutions occurred at three nucleotide positions: –3, –9, and –14 relative to the *leuB* AUG start codon (fig. S1). Ten amino acid replacements were found at three codons in the coenzyme binding pocket.

At first glance, the positive response to selection might suggest that coenzyme use by IMDH is unconstrained. Upstream substitutions in the Shine-Dalgarno sequence (positions –9 and –14), as well as a new AUG start codon (position –3) that replaces the less efficient GUG start codon, presumably derive their benefits through increases in expression because their kinetics are unchanged. Unexpectedly, however, beneficial amino acid replacements in the coenzyme binding pocket eliminate H bonds to the 2′-phosphate of NADP to cause striking reductions in NADP performance (Table 1). Although some mutants have improved NAD performance, others remain unchanged and several show reduced NAD performance. Isolated amino acid replacements outside the coenzyme binding pocket, which might have been expected to increase k_{cat}^{NADP} or to break the correlation in affinities between NADP and NADPH (K_m^{NADP} and K_i^{NADPH}), have no detectable functional effects (table S2, those associated with beneficial 5′-leader mutations in Table 1). No doubt they, along with 126 silent substitutions (table S1), hitchhiked through the genetic screen with the beneficial mutations.

Our results suggest that increases in expression are beneficial, whereas increases in NADP performance are not. This seeming paradox is resolved if there are no mutations capable of breaking the upper limit to k_{cat}^{NADP}, the correlation in affinities for NADP and NADPH, or the trade-off in coenzyme performance. With these constraints, and with reduced expression in the genetic screen, the phenotype-fitness map near LeuB[RKYVYR] remains flat with respect to increases in NADP performance (Fig. 2A). By contrast, severe losses of NADP performance are predicted to be beneficial as correlated reductions in the affinities for NADPH free up IMDH for use with abundant NAD. As predicted, all beneficial LeuB[RKYVYR] mutants have reduced affinities for both NADP and NADPH (Table 1). Unaffected by constraints, increases in expression are unconditionally beneficial (*18*). These results support the hypothesis that NADP-specific IMDHs function poorly in vivo because of strong inhibition by abundant NADPH. That reductions in NADP performance and increases in expression are both beneficial are the predicted consequences of a phenotype-fitness map constrained by an upper limit to k_{cat}^{NADP}, a correlation in affinities for NADP and NADPH, and a trade-off in coenzyme performance.

Breaking any one constraint would allow NADP-specific IMDHs to evolve. Yet no mutant increases k_{cat}^{NADP}, no mutant uncouples the affinities for NADP and NADPH, and no mutant breaks the trade-off in coenzyme performance. These conclusions are not the result of a selective screen that is too stringent. Of 35 colonies, representing 26 distinct mutants, that appeared after the 48-hour limit, 17 had no nucleotide substitutions in the 5′ leader sequence or amino acid replacements in LeuB[RKYVYR] (table S3). Amino acid replacements in the other mutants neither improved enzyme performance nor decreased NADPH inhibition (table S4). That no additional beneficial mutations were recovered with relaxed criteria demonstrates that the selective screen was not overly stringent.

Nor are the results a consequence of inadequate sampling of protein sequence space. Natural adaptive evolution fixes advantageous mutations sequentially (*22*–*24*). Indeed, experimental evolution demonstrates that advantageous double mutants in the evolved β-galactosidase of *E. coli* are not evolutionarily accessible and perforce must be accumulated as sequential advantageous mutations (*25*). Hence, screening

Table 1. Kinetic effects of amino acid replacements in LeuB[RKYVYR] isolated at 48 hours growth. Standard errors are <13% of estimates. Single-letter abbreviations for amino acid residues: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; Y, Tyr.

Enzyme	NADP			NAD			Preference (A/B)	K_i^{NADPH} (μM)
			Performance (A)			Performance (B)		
	K_m (μM)	k_{cat} (s^{-1})	k_{cat}/K_m (mM^{-1} s^{-1})	K_m (μM)	k_{cat} (s^{-1})	k_{cat}/K_m (mM^{-1} s^{-1})		
Site								
DDIAGR (wild type)	8400	4.10	0.4900	101	6.90	68.3200	0.007	254.30
RKYVYR	183	6.20	33.8800	4108	0.83	0.2000	169.400	9.90
Beneficial replacements								
K235N	3919	5.95	1.5200	6356	0.50	0.0800	19.000	129.00
K235N,–3(M),A60V	1744	5.06	2.9000	5395	0.44	0.0800	35.700	56.00
K235R	554	6.39	11.5000	3292	0.36	0.1100	106.100	26.00
K235R,E63V	658	6.75	10.3000	3748	0.46	0.1200	84.100	28.00
K289E*	3449	2.71	0.7900	4897	1.98	0.4000	2.000	133.50
K289E*,D317E	3554	3.62	1.0200	5580	2.09	0.3700	2.800	112.00
K289E*,D87Y,S182F	2551	2.54	1.0000	5750	3.65	0.6300	1.600	105.20
K289E*,F102L	3891	3.66	0.9400	4823	1.10	0.2300	4.100	131.90
K289M	2216	4.13	1.8600	4034	0.48	0.1200	15.500	78.60
K289M,F170L	1945	2.50	1.2900	2947	0.48	0.1600	8.100	87.20
K289N*	1141	6.32	5.5400	4997	1.14	0.2300	24.300	44.00
K289N*,R187H	1146	5.83	5.0900	3069	0.79	0.2600	19.600	44.70
K289N*,H367Q	1248	5.27	4.2200	4555	1.05	0.2300	18.300	57.80
K289T	1596	6.18	3.8700	4056	0.78	0.1900	20.400	71.60
K289T,Q157H	1696	5.66	3.3400	5038	0.93	0.1800	18.600	72.60
Y290C	988	5.21	5.2700	3792	1.02	0.2700	19.600	49.00
Y290C,R152C	910	3.15	3.4600	3844	0.90	0.2300	14.800	43.00
Y290D	10213	3.13	0.3100	9040	0.82	0.0900	3.400	344.00
Y290F*	1658	5.59	3.3700	3110	0.65	0.2100	16.000	59.70
Y290F,P97S,D314E	1097	4.64	4.2300	4158	0.71	0.1700	24.800	57.40
Y290N,N52T	2381	3.44	1.4400	10660	0.26	0.0200	59.500	90.00
Replacements with beneficial 5′-leader mutations								
RKYVYR	183	6.20	33.8800	4108	0.83	0.2000	169.400	9.90
–3(M)†,E66D	208	2.97	14.2800	5002	0.30	0.0600	238.000	11.90
–3(M)†,E66D,E331D	267	7.99	29.9000	3403	0.34	0.1000	296.900	14.00
E82D	221	5.44	24.6200	4735	0.35	0.0700	351.700	14.10
K100R,A229T,L248M	137	5.58	40.3700	4079	0.45	0.1100	370.300	11.50
G156R,K289R,Y311H	292	5.40	18.4900	4464	0.54	0.1200	144.800	17.40
E173D	219	6.39	29.1800	5304	0.89	0.1700	171.600	6.60
Y337N,G131	171	5.71	33.3900	3367	0.24	0.0700	468.500	8.00
Y337H,P85S,E181K	318	5.21	16.3800	2409	0.22	0.0900	183.600	12.80

*Switch from NADP to NAD requires two base substitutions in one codon. This is a possible transitional amino acid produced by a single base substitution (*11*). †The –3(M) designates a G to A substitution at base –3 that creates a new start codon.

all single substitutions is a sufficient sampling of protein sequence space for robust evolutionary conclusions. We estimate that only 0.04 advantageous amino acid replacements are missing from the mutant *leuB[RKYVYR]* library (*18*). We conclude that mutations capable of breaking the limit, the correlation, or the trade-off are unlikely to ever be fixed in populations because they are exceedingly rare (they may not exist), because they are minimally advantageous, or both.

The two remaining ways to evolve an NADP-specific IMDH are to reduce intracellular NADPH pool and, as our results show, to increase expression. Reducing intracellular NADPH relieves the inhibition but, as experiments deleting sources of NADPH show (*13*), the disruption to the rest of metabolism costs far more than the benefit to be gained. The phenotype-fitness map (Fig. 1C) imposes a law of diminishing returns such that LeuB[RKYVYR] must be expressed above wild-type levels by a factor of 100 to overcome the inhibition by NADPH (*18*). Diverting resources away from other metabolic needs toward compensatory protein synthesis would impose a protein burden (*26*–*29*) sufficient to prevent the evolution of NADP-specific IMDHs.

The production of unnatural phenotypes, by artificial selection or molecular engineering, is not sufficient to conclude that evolutionary constraints are absent entirely. Rather, potential constraints underlying a conserved phenotype can be identified from the relationships among genotype, phenotype, and fitness that define an adaptive landscape. Experimental evolution can then be used to test their existence. Using this approach, we have shown how certain structure-function relationships in IMDH have constrained its coenzyme phenotype since the last common ancestor.

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30. Supported by NIH grant GM060611 (A.M.D.). We thank three anonymous reviewers whose constructive criticisms we found invaluable.

Supporting Online Material

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4 August 2006; accepted 20 September 2006
10.1126/science.1133479

An Essential Role for LEDGF/p75 in HIV Integration

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Chromosomal integration enables human immunodeficiency virus (HIV) to establish a permanent reservoir that can be therapeutically suppressed but not eradicated. Participation of cellular proteins in this obligate replication step is poorly understood. We used intensified RNA interference and dominant-negative protein approaches to show that the cellular transcriptional coactivator lens epithelium–derived growth factor (LEDGF)/p75 (p75) is an essential HIV integration cofactor. The mechanism requires both linkages of a molecular tether that p75 forms between integrase and chromatin. Fractionally minute levels of endogenous p75 are sufficient to enable integration, showing that cellular factors that engage HIV after entry may elude identification in less intensive knockdowns. Perturbing the p75-integrase interaction may have therapeutic potential.

Integration enables human immunodeficiency virus type 1 (HIV-1) to establish a permanent genetic reservoir that can initiate new virion production, evade immune surveillance, and replicate through mitosis. Integrated proviruses that persist in long-lived T cells ensure rapid HIV recrudescence if antiviral drugs are withdrawn. Integration is catalyzed by the viral integrase (IN). When expressed as a free protein in cells rather than within its normal context as an intravirion cleavage product of the HIV Gag-Pol precursor, IN becomes tethered to chromatin by cellular lens epithelium–derived growth factor/p75 (p75) (*1*–*3*), which is a transcriptional coactivator (*4*). Accordingly, both proteins display tight colocalization with chromatin throughout the cell cycle; short hairpin RNA (shRNA)–mediated knockdown of p75 untethers IN, redistributing it from an entirely nuclear to an entirely cytoplasmic location (*3*). Molecular tethering results from specific linkages formed by p75's discrete functional modules: the N-terminal Pro-Trp-Trp-Pro (PWWP) and A/T-hook elements bind to chromatin (*5*), and a C-terminal integrase-binding domain (IBD) binds to IN (*6*, *7*). p75 also protects the HIV-1 IN protein from rapid degradation in the 26S proteasome (*8*). In the bona fide viral context, drastic knockdown of p75 changed the genomic pattern of HIV-1 integration by reducing the viral bias for active genes, which suggests that p75 influences integration targeting (*9*). However, changes in overall levels of HIV integration and replication have been either absent or modest, and single-cycle infection analyses in cell lines have consistently detected no effect, which has led to questions about the overall importance of p75 in the viral life cycle (*3*, *7*, *9*–*12*).

Previously, we observed that a nuclear localization signal–mutant p75 protein became constitutively chromatin-trapped in stable cell lines (*7*). In the present work, we hypothesized the existence in previous severely RNA interference (RNAi)–depleted HIV-susceptible cells of a very small yet virologically potent chromatin-associated p75 residuum. We reasoned that a fractionally minute residual pool with a spatially favorable location (colocalized with chromatin) could explain the inability to demonstrate substantial, reproducible impairments in integration or viral replication in cells lacking detectable p75. Such a reservoir would be inadequate to affect observable properties of ectopically expressed IN but might be sufficient to engage the vastly less abundant incoming viral preintegration complex.

To test this hypothesis, we performed subcellular fractionation and interrogated chromatin, using a deoxyribonuclease (DNase) I– and salt-based extraction protocol (*13*). These methods

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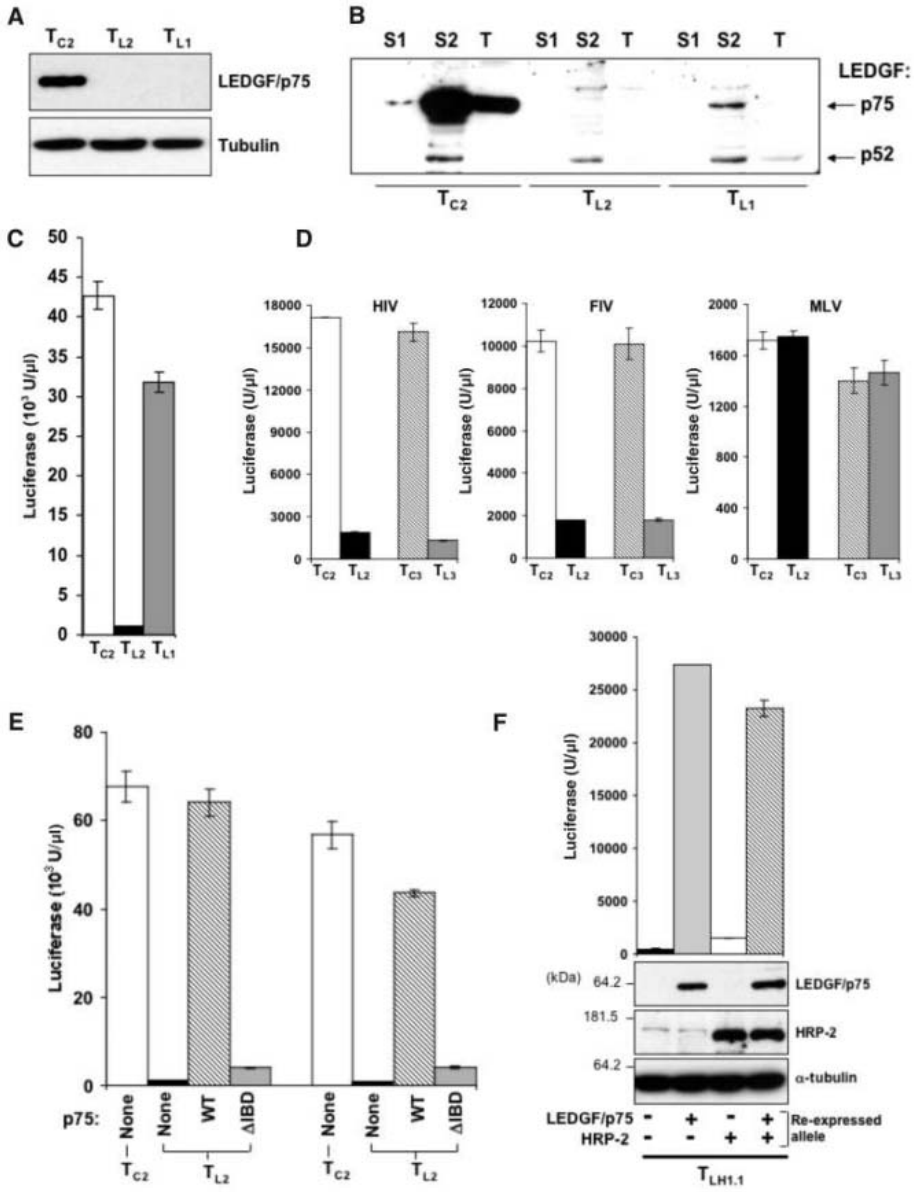

Fig. 1. Eradication of detectable p75 from chromatin and susceptibility to retroviral infection. Polyclonal SupT1 cell lines were derived by ilvRNAi (*13*). See fig. S1A (panel i) for construct structures and (*13*) for the cell line nomenclature system. Lentiviral vectors expressed either a control (T_C cells) or a p75-specific shRNA (T_L cells). T_{L1} and T_{L2} are two independently derived polyclonal T_L cell lines. Seven T_C lines (T_{C1} to T_{C7}), independently derived in parallel for pairwise comparison with any given T_L line, showed HIV-1 susceptibility equivalent to parental SupT1 cells. T_{C2} was used in this experiment. (**A**) Detection of p75 in whole-cell lysates by immunoblotting with p75 monoclonal antibody (mAb). (**B**) Detection of p75 in subcellular fractions by immunoblotting with p75 mAb. T, total cell lysate; S1, Triton-X100–extractable, non–chromatin-bound fraction; S2, Triton-X100–resistant chromatin-bound fraction released by further DNase I– and salt-based extraction. p75 was detected in abundance in S2 in the absence of p75-specific RNAi (T_C cells); only radical S2 depletion blocked viral infection. See figure 3 of (*5*) for the fractionation scheme and method validation. (**C**) Analysis of single-round HIV reporter virus infection. Cells were infected with HIVluc, and luciferase enzymatic activity was determined 5 days later. (**D**) p75 eradication from the S2 fraction blocks HIV-1 and FIV infection but not MLV infection. S2FN cell lines were infected in parallel with three different retroviral vectors (HIV-1, FIV, and MLV), and luciferase activity was determined 5 days later. (**E**) p75 reexpression rescues HIV infectivity in S2FN T cell lines but $p75^{IBD–}$ does not. p75 [wild-type (WT) or IBD-deleted (ΔIBD)] was reexpressed in S2FN cells by gamma-retroviral vector expression of shRNA-resistant alleles (fig. S1B). Relevant immunoblotting is shown in fig. S5. (**F**) Differential effect of p75 versus HRP-2 reexpression. A single cell clone of T_{LH1}, $T_{LH1.1}$, was back-complemented with p75, HRP-2, or both and reexpression was verified by immunoblotting. Five additional clones ($T_{LH1.2}$ to $T_{LH1.6}$) showed the same results. Error bars in (C) to (F) represent SD of duplicate determinations.

detected a chromatin-associated p75 residuum in virally permissive knockdown cell lines. We then developed a new strategy to eradicate the residual pool, using RNAi with intensified lentiviral vector-based RNAi (ilvRNAi) [panel i in fig. S1A and (*13*)]. Human $CD4^+$ T cells with no immunoblot-detectable p75 in whole-cell lysates [Fig. 1A, T_{L1} cells; see (*13*) for nomenclature] but with a scant detectable residue of p75 in the DNase I– and salt-extractable chromatin fraction (Fig. 1B, S2 fraction) were marginally impaired for single-cycle HIV infection (Fig. 1C). In contrast, in S2 fraction–negative (S2FN) cells in which ilvRNAi resulted in undetectable p75 in the S2 fraction as determined by direct Western blotting (Fig. 1B, T_{L2} cells) or immunoprecipitation (fig. S2A), HIV luciferase reporter virus (HIVluc) infection was reduced to 3.5% of control SupT1 cells transduced equivalently with lentiviral vectors encoding a control shRNA (Fig. 1C). The requirement for radical depletion of p75 to block infection was observed repeatedly in independently derived cell lines with both mCherry- and enhanced green fluorescent protein (eGFP)–marking lentiviral vectors (n = 7 experiments; mean fold inhibition, 28 ± 5%). In 46 experiments conducted with two independently derived S2FN T cell lines, the mean inhibition compared to control lines was 31-fold (fig. S3). The required RNAi intensification was also evident at the mRNA level: Only ilvRNAi-derived cells in which mRNA was reduced to less than 3% of baseline levels were S2FN and resistant to infection (fig. S2B). Equivalent transduction with the p75-specific shRNA and control shRNA ilvRNAi vectors was documented by both Southern blotting for vector DNA and marker protein fluorescence (fig. S4, A and B). The control vector, which differed from the p75-specific vector only within the 21 base pairs of the shRNA hairpin, had no effect on susceptibility to HIV infection in any of seven different ilvRNAi-derived cell lines.

Feline immunodeficiency virus (FIV), a non-primate lentivirus with a p75-interacting IN (*3*, *14*), was similarly blocked by p75-specific ilvRNAi (Fig. 1D). In contrast, a gamma retrovirus [murine leukemia virus (MLV)] was completely unimpaired in S2FN cell lines (Fig. 1D), a result consistent with the lack of interaction between MLV IN and p75 (*3*, *14*). This lentiviral specificity enabled us to use MLV vectors to reexpress p75 (fig. S5), which fully rescued susceptibility to HIV-1 (Fig. 1E) and FIV (fig. S6A) but had no effect on gamma-retroviral infection (fig. S6B). Moreover, no rescue was seen when p75 had a specific deletion of the IBD, establishing that this component of the molecular tether is needed (Fig. 1E and fig. S5, panel iii). The results were corroborated by analyses of individual cell clones of ilvRNAi-derived cell lines, where 25- to 65-fold lentiviral-specific inhibition compared to control lines was observed (fig. S7, A and B).

Additional specificity was revealed when we targeted the p75-related protein hepatoma-derived growth factor–related protein 2 (HRP-2), which

shares the p75 IBD and binds to HIV-1 IN (*6*, *7*). HRP-2 can also rescue nuclear targeting of IN in p75-deficient cells (*7*). However, in contrast to p75, HRP-2 is fully extractable in Triton-X100 and does not constitutively tether IN to chromatin (*7*) or detectably influence integration-site patterns (*9*). HRP-2–specific ilvRNAi had no effect on HIV infection, whether introduced alone (fig. S7C, T_H lines) or additively to p75-specific ilvRNAi (T_{LH1} cells and six clones, $T_{LH1.1}$ to $T_{LH1.6}$) (Fig. 1F and fig. S7C). p75 rescued double-knockdown cells but HRP-2 did not (Fig. 1F). FIV and MLV were also completely unaffected by HRP-2 ilvRNAi; all viral infection impairments were again both lentiviral-specific and attributable only to p75 (fig. S7D).

We also examined productive replication of HIV-1 (Fig. 2). Viral replication was blocked in S2FN cells at both low (0.001 to 0.01) and high (0.1) multiplicity of infection (MOI) when either polyclonal or clonal lines were challenged with replication-competent HIV-1 NL4-3, an infectious molecular clone. Again, p75 fully rescued viral replication (Fig. 2 and fig. S8), whereas HRP-2 did not (Fig. 2B).

We next determined whether any mechanisms could be assigned to the virus producer cell [similar to effects seen with the negatively acting factor APOBEC3G (*15*)] or to transcriptional effects. However, the origin of challenge HIV in S2FN versus control T cells had no influence on infectivity. All effects were solely attributable to target cell p75 status for both single-cycle HIV-1 vectors and replication-competent HIV-1. We also depleted p75 with ilvRNAi after HIVluc infection, which produced no change in viral expression. Conversely, reexpression of p75 in S2FN cells after HIVluc infection yielded no change in luciferase or p24 levels. To further test for transcriptional or promoter-specific effects, we infected T_C and T_L cells and clones with the internally promoted reporter virus HIVc-luc (fig. S1C). HIVc-luc yielded the same phenotype as HIVluc, confirming that p75-specific ilvRNAi does not interfere with Tat protein transactivation (fig. S9). In addition, MLV was uninhibited in S2FN cells, whether reporter expression was driven by the native retroviral U3 or an internal cytomegalovirus promoter.

To further investigate the mechanism of action of p75 in the viral life cycle, we tested the functional capabilities of a chromatin-binding mutant, $p75^{P-A-}$ (fig. S1B). $p75^{P-A-}$ lacks PWWP and A/T-hook domains, which compose the N-terminal chromatin-binding link of the molecular tether (*5*). Like wild-type p75, $p75^{P-A-}$ is nuclear and binds IN at the IBD, but it is not chromatin-bound and therefore it does not tether IN to chromatin (*5*). An IN stability rescue assay showed that $p75^{P-A-}$ does retain the function of protecting IN from proteasomal degradation (fig. S10). However, the HIV infection–rescuing function is lost (Fig. 3A), showing that such rescue requires not only the IBD interaction but also the IN-to-chromatin tethering capacity. Consistent with this

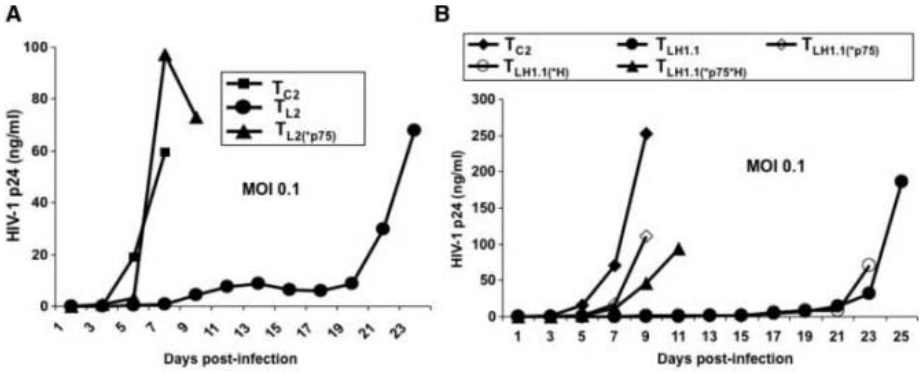

Fig. 2. HIV-1 replication in cell lines and clones with and without rescue of p75- and/or HRP-2 RNAi. Each line or clone was compared to its respective back-complement. Equivalent CD4 and CXCR4 expression were verified by fluorescence-activated cell sorting analyses (fig. S4C). Cells were infected with HIV-1 clone NL4-3 at three different MOIs (0.1, 0.01, and 0.001). Experiments at the two higher MOIs are shown. (**A**) MOI = 0.1, polyclonal T_{L2} cell line. (**B**) Double-knockdown single cell clone $T_{LH1.1}$ was back-complemented with p75, HRP-2, or both. Cells shown here were infected at an MOI value of 0.1. Lower MOI infection values (0.01 and 0.001) produced proportionate delays; for example, at an MOI value of 0.01, p24 values reached 20 ng/ml in T_{C2} and $T_{LH1.1}$ cells on days 7 and 57, respectively. This viral replication delay was rescued by p75 reexpression (p24 values reached 9.2 ng/ml on day 9).

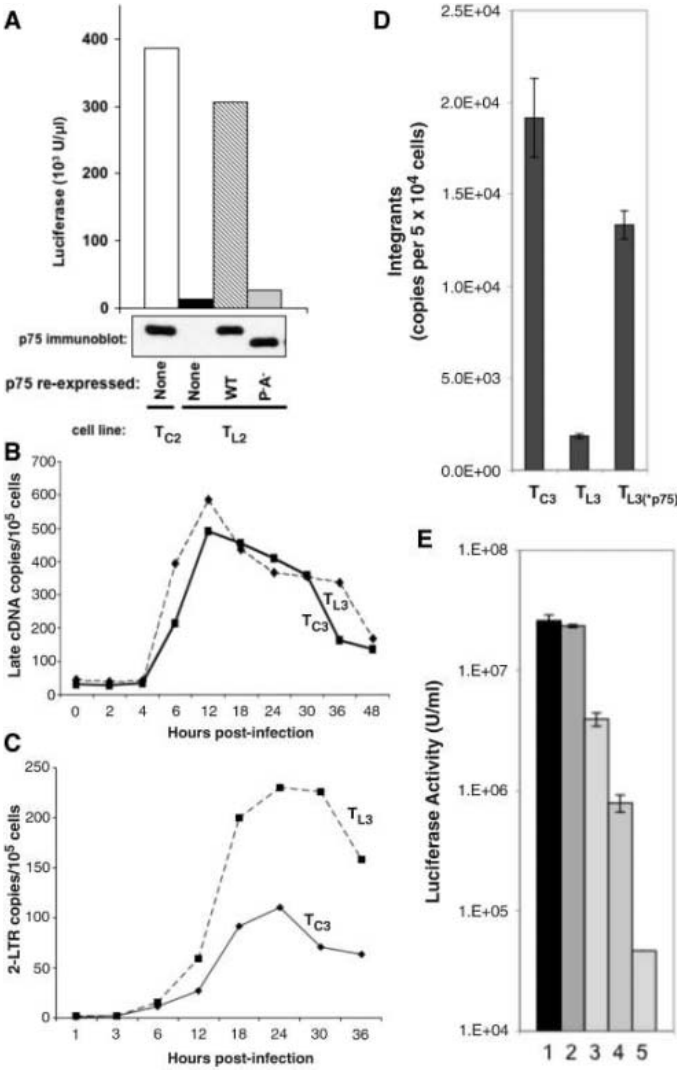

Fig. 3. Mechanism of p75 action. (**A**) $p75^{P-A-}$ did not rescue HIV-1 infection. Luciferase activity was measured 5 days after HIVluc infection. (**B** to **D**) Analyses of viral DNA forms in cells infected with HIVluc. (B) Late cDNA. (C) 2-LTR circles. (D) *Alu*-PCR results 14 days after infection. (**E**) Dominant-negative inhibition by the p75 IBD. Each line was derived from SupT1 cells with a single lentiviral vector that expressed either eGFP or eGFP that was fused in frame to the IBD, with or without an shRNA cassette (fig. S1A, panel ii). p75 IBD fragments were wild type or contained a single Asp→Asn mutation at p75 residue 366. The five single lentiviral vectors that were used to derive the lines contained the following expression elements: lane 1, control shRNA with GFP; lane 2, GFP-IBD (D366N); lane 3, GFP-IBD (WT); lane 4, p75 shRNA with GFP; lane 5, p75 shRNA with GFP-IBD (WT). Cells were infected with HIVluc and analyzed 5 days later for luciferase activity. U, units. Error bars in (D) and (E) represent SD of duplicate determinations.

evidence that the mechanism involves interaction with IN at chromatin, the defect for HIV infection in S2FN cells was determined to be at the integration step by real-time quantitative polymerase chain reaction (PCR) for stage-specific viral and viral-host junction DNAs (Fig. 3, B to D). Full-length reverse transcription products were equivalent at multiple time points in control and S2FN cells (Fig. 3B). In contrast, 2–long terminal repeat (LTR) circles were increased in S2FN cells (Fig. 3C); this finding is consistent with a block to integration with consequent routing of nuclear cDNA to circularization. In direct support of this idea, *Alu*-PCR products were reduced by more than 10 times in S2FN T cells (Fig. 3D). Southern blotting of genomic DNA with reporter virus–specific probes for an internal viral fragment (fig. S11A) and viral-host DNA junctions (fig. S11B) corroborated the integration block.

Reciprocal passages of outgrowth viruses between parental and knockdown cell lines did not yield evidence for viral adaptation to the lack of p75 in S2FN cells, indicating that the eventual viral outgrowth resulted from slow accrual of wild-type virus encountering stringent restriction, rather than mutational adaptation. These results suggest that the p75-IN interaction may be a target for small-molecule or dominant-negative therapeutic strategies. To investigate the dominant-negative concept and to further confirm the role of p75, we expressed an eGFP-IBD fusion protein in which amino acids 340 to 417 of p75 were fused in frame to the C terminus of eGFP (fig. S1A, panel ii). eGFP-IBD, which interacts with IN in cells (*7*), also protected IN from proteasomal degradation and had a seven-fold inhibitory effect on single-round HIV-1 infection in p75–wild-type cells (Fig. 3E). Introduction of a single amino acid mutation, $Asp^{366} \rightarrow Asn^{366}$ (D366N), which abrogates IN-IBD interaction (*16*), had no effect. Combining p75-specific ilvRNAi and fusion protein expression produced a 555-fold reduction in HIV-1 susceptibility (Fig. 3E).

Our studies show that p75 acts through a tethering mechanism as a potent cofactor for HIV-1 integration. More generally, we conclude that the cellular factors that engage the incoming HIV substructure can have virological efficacy in low concentrations and may be missed by RNAi screens of lower intensity. The apparent lack of redundancy, with p75 but not HRP-2 being required for integration, may indicate a potential therapeutic opportunity. Small molecules that could disrupt the interface, and perhaps dominant-negative approaches, are of interest for further study. Given the skewed HIV integration pattern we observed previously in adherent cells that knocked down for p75 yet were still S2 fraction–positive, in which the bias for integrating into active genes was reduced (*9*), it will also be interesting to determine the genomic pattern of the low-level integration that occurs in S2FN T cells.

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17. We thank M. Allen for assistance with lentiviral vector construction and other laboratory members for helpful discussions. T cell lines were obtained from the NIH AIDS Research and Reference Reagent Program. The laboratory is supported by grants to E.M.P. from NIH and the John H. Tietze Foundation Research Trust.

Supporting Online Material

www.sciencemag.org/cgi/content/full/1132319/DC1
Materials and Methods
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10 July 2006; accepted 29 August 2006
Published online 7 September 2006;
10.1126/science.1132319
Include this information when citing this paper.

Dynamic Nuclear Actin Assembly by Arp2/3 Complex and a Baculovirus WASP-Like Protein

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Diverse bacterial and viral pathogens induce actin polymerization in the cytoplasm of host cells to facilitate infection. Here, we describe a pathogenic mechanism for promoting dynamic actin assembly in the nucleus to enable viral replication. The baculovirus *Autographa californica* multiple nucleopolyhedrovirus induced nuclear actin polymerization by translocating the host actin-nucleating Arp2/3 complex into the nucleus, where it was activated by p78/83, a viral Wiskott-Aldrich syndrome protein (WASP)–like protein. Nuclear actin assembly by p78/83 and Arp2/3 complex was essential for viral progeny production. Recompartmentalizing dynamic host actin may represent a conserved mode of pathogenesis and reflect viral manipulation of normal functions of nuclear actin.

Baculoviruses are enveloped, double-stranded (ds) DNA viruses that primarily infect the larvae of lepidopteran insects. They are widely used as protein expression vectors and are being developed for mammalian gene delivery and as environmentally benign pesticides (*1*). The best-studied baculovirus is *Autographa californica* multiple nucleopolyhedrovirus (AcMNPV). During infection, AcMNPV induces a series of actin rearrangements in host cells, the most striking of which is the accumulation and polymerization of actin within the nucleus (*2*, *3*). Monomeric actin (G-actin) is driven to accumulate in the nucleus by early viral gene products (*4*), and nuclear actin is polymerized into filaments (F-actin) by the products of late viral genes (*2*, *4*). Both steps are essential for progeny production (*5*–*7*). Actin is also present in the nucleus in uninfected cells, even in polymeric form (*8*, *9*), and plays a role in diverse nuclear processes (*10*). However, little is known about the active forms and the regulation of nuclear actin. We investigated the process of nuclear actin polymerization induced by AcMNPV.

To establish the timing of nuclear recruitment and polymerization of actin, we infected *Trichoplusia ni* TN-368 cells expressing either enhanced green fluorescent protein (EGFP)–actin or mCherry-actin with AcMNPV and followed actin localization by time-lapse microscopy. Diffuse fluorescent actin began to accumulate in nuclei at 10 to 20 hours post-infection (hpi), and an apparent equilibrium between nuclear and cytoplasmic actin was reached within 2 hours (Fig. 1A and movies S1 to S3). The initial diffuse signal corresponded to G-actin, because it did not react with the F-actin probe phalloidin in fixed cells (*4*) and was not disrupted by the actin depolymerizing agent latrunculin A (latA) in live cells. Nuclear G-actin began to polymerize 2.0 ± 0.4 hours (mean ± SD, $n = 7$) after nuclear entry, as indicated by the conversion of diffuse actin into distinct structures and the reversion of these structures back to diffuse signal within minutes after latA treatment (Fig. 1A and movie S1). Polymerization proceeded rapidly until most of the cytoplasmic actin accumulated within the nucleus (Fig. 1A and movies S1 to S3). The uniformity of timing between nuclear recruitment and polymerization of actin indicates that actin rearrangements are precisely controlled.

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We next assessed the dynamics of nuclear F-actin by monitoring fluorescence recovery after photobleaching (FRAP) in infected TN-368 cells expressing EGFP-actin. FRAP was performed by photobleaching a small region in the nucleus during the peak of viral replication (12 to 24 hpi). In most cells (63%), fluorescence recovered quickly, with a mean half-time of 22 ± 6 s (n = 10) (Fig. 1, B and C, and movie S4), similar to the rate in highly dynamic structures in migrating cells (*11*). When nuclear actin filaments were stabilized with the depolymerization inhibitor jasplakinolide (jasp), fluorescence did not recover, demonstrating that recovery was due to filament turnover (Fig. 1C). Conversely, when filaments were depolymerized by using latA, fluorescence loss in photobleaching (FLIP) was observed in the nucleus, presumably due to rapid diffusion of EGFP-actin monomers (movie S5). In some cells (37%), nuclear F-actin failed to recover fluorescence after photobleaching, suggesting that it could vary from a highly dynamic to a stable state. Nevertheless, dynamic actin was essential for viral replication, because treatment of infected cells with jasp prevented production of budded virus (Fig. 1D). Given the rapid turnover of nuclear F-actin in infected cells, we reasoned that factors regulating cytoplasmic actin assembly might be involved in NPV-induced nuclear actin dynamics.

One such regulator is the Arp2/3 complex, which is activated to nucleate branched actin filaments by proteins called nucleation-promoting factors (NPFs) (*12*). Diverse NPV species encode a capsid-associated protein, called p78/83 in AcMNPV, that contains domains conserved in Wiskott-Aldrich syndrome protein (WASP) family NPFs (*13*). These include proline-rich regions, WASP–homology 2 (WH2 or W) domains that bind G-actin, and a connector and acidic region (CA) that binds Arp2/3 complex (Figs. 2A and 3A and fig. S1). Because the WCA fragment of NPFs is sufficient to activate the Arp2/3 complex (*12*), we purified a truncation of p78/83 containing the WCA region (p78-WCA) and assessed whether it could activate Arp2/3 in vitro. Purified p78-WCA stimulated actin polymerization with Arp2/3 complex in a concentration-dependent manner but had no effect in the absence of Arp2/3 (Fig. 2B). Moreover, p78-WCA induced the organization of filaments into y branches, a hallmark of Arp2/3 activation (fig. S2). Capsid-associated p78/83 also activated Arp2/3 complex to accelerate actin polymerization but had no effect in the absence of Arp2/3 (Fig. 2C). Thus, p78/83 is a viral NPF for the Arp2/3 complex.

The biochemical activity of p78/83 and Arp2/3 complex suggested that they could nucleate actin polymerization during infection. To learn where these factors acted, we determined their localization in infected TN-368 cells. Both Arp2/3 complex and p78/83 were localized in the nucleus by 22 hpi (Fig. 2D). Most cells exhibiting nuclear p78/83 and Arp2/3 also showed strong nuclear F-actin staining (Fig. 2E). Neither Arp2/3 complex (Fig. 2D) nor exogenously expressed p78/83 (fig. S3) localized to the nucleus in uninfected cells, indicating that both required other viral products for nuclear accumulation. The localization of host Arp2/3 complex and p78/83 in infected cells suggests that they function in the nucleus to initiate actin polymerization.

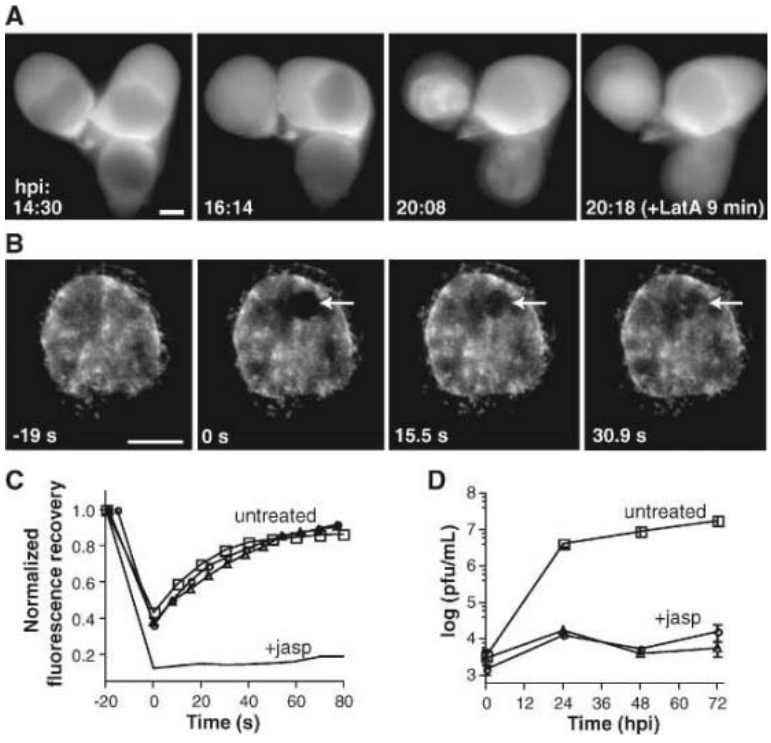

Fig. 1. AcMNPV induces dynamic nuclear actin polymerization that is required for viral replication. (**A**) EGFP-actin fluorescence in live, infected TN-368 cells imaged at the indicated times (in hours:minutes) post-infection [multiplicity of infection (MOI) of 20]. Scale bar indicates 10 μm. (**B**) EGFP-actin fluorescence in the nucleus of a TN-368 cell at 12 hpi (MOI = 20) at the indicated times before and after photobleaching. Arrow indicates bleached region. Scale bar, 10 μm. (**C**) Fluorescence recovery versus time in cells photobleached at 12 (triangles), 18 (circles), or 24 hpi (squares) or at 24 hpi in the presence of jasplakinolide (solid line; 1 μM, added at 20 hpi). (**D**) Replication of AcMNPV in Sf9 cells in the absence (squares) or the presence of 1 μM jasplakinolide added at 0 (triangles) or 15 hpi (circles). pfu, plaque-forming units.

Nuclear F-actin is essential for NPV replication (*5*, *7*). The *p78/83* gene is also essential (*14*), consistent with the hypothesis that p78/83 NPF activity is required for nuclear actin polymerization and progeny production. To test this, we mutated conserved residues in the p78/83 CA region (Fig. 3A) that, when mutated in host NPFs, caused defects in Arp2/3 activation (*15*, *16*). Purified mutant p78-WCA proteins exhibited actin polymerizing activities in vitro ranging from wild-type [for $Asp^{364}\rightarrow Ala^{364}$ (D364A)] to moderately defective [$Ile^{358}\rightarrow Ala^{358}$ (I358A) and $Asp^{384}Glu^{385}\rightarrow Ala^{384}Ala^{385}$ (DE384-5AA)] and to severely defective [Trp387→Ala387 (W387A) and $Arg^{368}Arg^{369}Arg^{370}\rightarrow Ala^{368}Ala^{369}Ala^{370}$ (RRR368-7AAA)] (Fig. 3B), similar to the corresponding host WASP mutants (*15*, *16*).

To correlate p78/83 activity in vitro with its role in viral replication, we introduced each of the above mutations into the viral genome. We constructed an AcMNPV E2 baculovirus shuttle vector (bacmid), called WOBpos, that could be propagated in *Escherichia coli* even when it contained lethal mutations (fig. S4). WOBpos-derived AcMNPV was equivalent to wild type with respect to replication in cells and infectivity in the insect host (fig. S4). We engineered *p78/83* point mutations and a deletion mutation (*Δp78/83*) by homologous recombination with WOBpos in *E. coli* (fig. S4). Equal amounts of wild-type and mutant bacmids were transfected into *Spodoptera frugiperda* Sf9 cells, and culture supernatants were tested for infectious virus. Of the mutants, only D364A (wild-type activity) and I358A (moderately defective) yielded viable progeny (table S1). D364A replicated with kinetics indistinguishable from those of the wild type, whereas I358A showed delayed viral production and reduced titer (Fig. 3C and table S1). The remaining mutants failed to produce progeny virus (table S1), in correlation with their severely reduced NPF activities. Viral viability could be rescued by cotransfection with a plasmid expressing wild-type p78/83 (table S1). Furthermore, dsRNA-mediated silencing of the ARPC3/p21 subunit of Arp2/3 complex (to 50% of normal amounts) caused a substantial reduction in viral titer (fig. S5). Thus, the ability

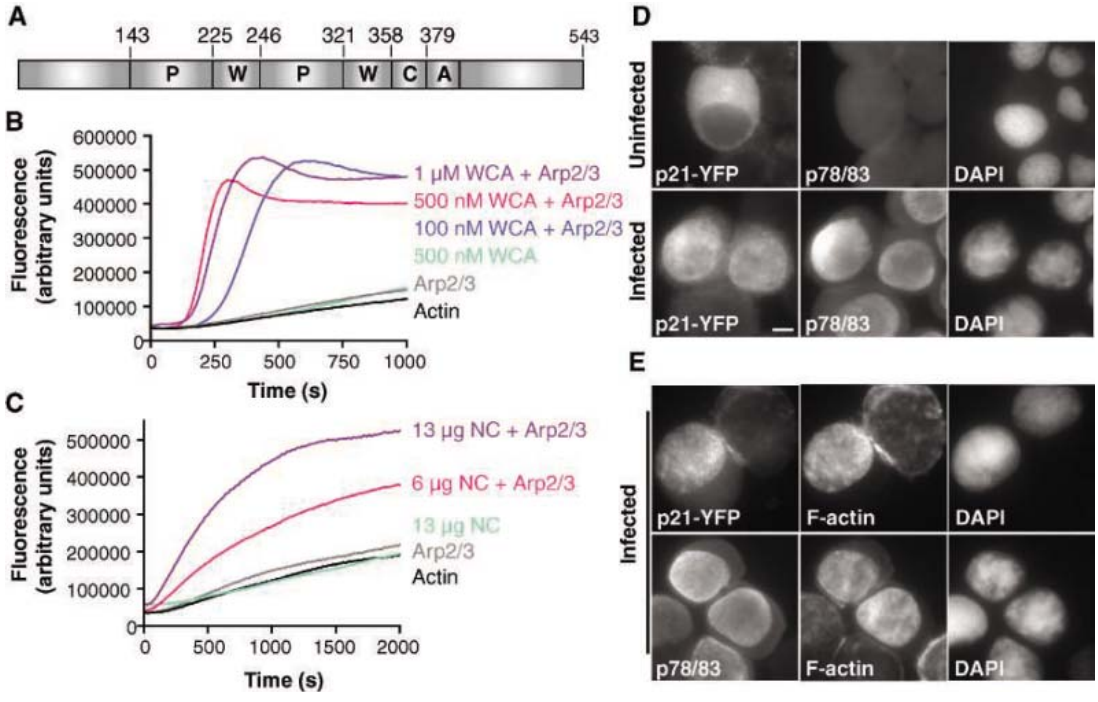

Fig. 2. p78/83 activates Arp2/3 complex in vitro and localizes with Arp2/3 complex and F-actin in the nucleus in infected cells. (**A**) Domain organization of AcMNPV p78/83 depicting proline rich (P), WH2 (W), and connector and acidic (C and A) regions. (**B** and **C**) Pyrene-actin polymerization assays with 2 μM actin (7% pyrene labeled), 20 nM Arp2/3 complex, and indicated concentrations of glutathione *S*-transferase (GST)–p78–WCA or AcMNPV nucleocapsid (NC). (**D**) Arp2/3 complex and p78/83 in infected or uninfected TN-368 cells fixed at 22 hpi. Arp2/3 complex was stained by transfection with a plasmid expressing yellow fluorescent protein (YFP)–tagged *T. ni* ARPC3/p21 (p21-YFP) and by immunofluorescence using GFP antibodies. p78/83 was visualized by immunofluorescence using a p78/83 antibody (fig. S3). Scale bar, 10 μm. (**E**) Arp2/3 complex, p78/83, and actin in infected TN-368 cells either transfected with p21-YFP (top) or not transfected (bottom). Cells were fixed at 22 hpi and stained with 4′,6′-diamidino-2-phenylindole (DAPI), rhodamine- (top), or Alexa 488 (Invitrogen, Carlsbad, CA)–phalloidin (bottom) and GFP or p78/83 antibodies.

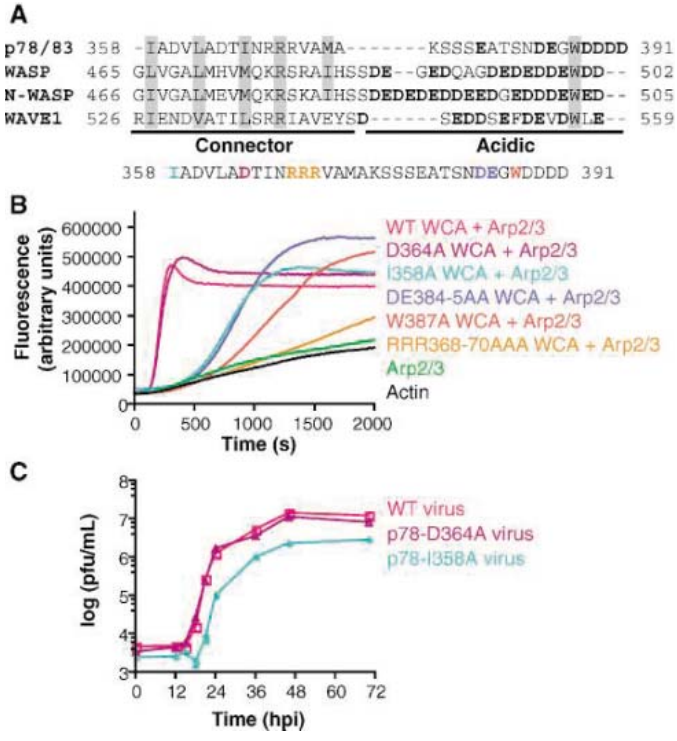

Fig. 3. Mutations in p78/83 cause defects in NPF activity and viral replication. (**A**) Alignment of the CA region of AcMNPV p78/83 with human WASP, N-WASP, and WAVE/Scar1 (WASP family verprolin-homologous protein/suppressor of cyclic adenosine monophosphate). Conserved residues are outlined in gray, and acidic A region residues are bold. Residues in p78/83 that were mutated to alanine are colored. (**B**) Pyrene-actin polymerization assays performed as in Fig. 2B with 500 nM of the indicated GST-p78-WCA proteins. (**C**) Growth of wild-type (WT) and viable p78/83 mutant viruses in Sf9 cells.

of p78/83 to activate Arp2/3 complex is essential for AcMNPV replication.

To determine whether p78/83 activation of Arp2/3 complex is required for nuclear actin polymerization, we observed the distributions of F-actin, p78/83, and Arp2/3 complex in TN-368 cells transfected with wild-type or p78/83 mutant bacmids. Mutant p78/83 proteins were produced at quantities similar to those of wild type and localized to nuclei (Fig. 4A and fig. S6). Arp2/3 complex also localized to nuclei in cells transfected with the *Δp78/83* mutant (fig. S7), indicating that p78/83 is not necessary for its nuclear translocation. We never observed accumulation of nuclear F-actin in cells transfected with *Δp78/83*, W387A, DE384-5AA, or RRR368-70AAA mutants, which had low NPF activity and were inviable (Fig. 4, A and B; fig. S6; and table S1). Nuclear F-actin staining was observed, however, in cells transfected with wild-type bacmid and with the viable D364A and I358A mutants. Thus, p78/83 activation of Arp2/3 complex is necessary for nuclear actin polymerization during NPV infection. p78/83 and Arp2/3 complex were not sufficient, however, because artificially targeting each to the nucleus in uninfected cells by appending a nuclear localization signal did not cause nuclear actin polymerization (fig. S7), probably because other viral factors are required for nuclear G-actin accumulation (*4*).

To investigate the mechanism by which p78/83 and Arp2/3 participate in viral replication, we examined virions in cells at 48 hours posttransfection (hpt) with wild-type or DE384-5AA mutant bacmids by using electron microscopy. The wild-type bacmid produced characteristic preoccluded (Fig. 4C) and occluded virions containing multiple nucleocapsids neatly aligned and surrounded by tight membranous envelopes. Although the DE384-5AA mutant bacmid produced many apparently normal nucleocapsids, there was a higher frequency of nucleocapsids of aberrant length (Fig. 4C). We also observed striking defects in virion organization. Most mutant nucleocapsids lacked envelopes or were misaligned within envelopes, and there were abundant membranes without associated nucleocapsids. These observations point to a key role

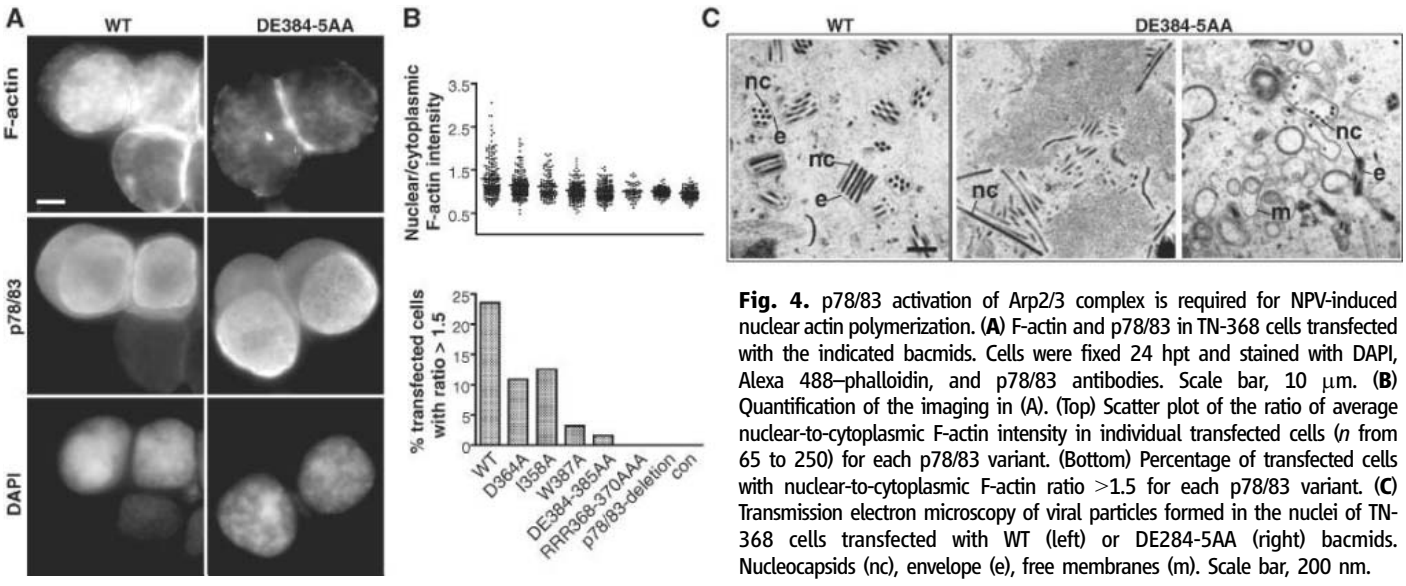

Fig. 4. p78/83 activation of Arp2/3 complex is required for NPV-induced nuclear actin polymerization. (**A**) F-actin and p78/83 in TN-368 cells transfected with the indicated bacmids. Cells were fixed 24 hpt and stained with DAPI, Alexa 488–phalloidin, and p78/83 antibodies. Scale bar, 10 μm. (**B**) Quantification of the imaging in (A). (Top) Scatter plot of the ratio of average nuclear-to-cytoplasmic F-actin intensity in individual transfected cells (*n* from 65 to 250) for each p78/83 variant. (Bottom) Percentage of transfected cells with nuclear-to-cytoplasmic F-actin ratio >1.5 for each p78/83 variant. (**C**) Transmission electron microscopy of viral particles formed in the nuclei of TN-368 cells transfected with WT (left) or DE284-5AA (right) bacmids. Nucleocapsids (nc), envelope (e), free membranes (m). Scale bar, 200 nm.

for nuclear actin polymerization in coordinating nucleocapsid morphogenesis and membrane-capsid interactions during virion assembly.

AcMNPV has evolved exquisite control over the actin cytoskeleton of its host cell, manipulating both activity and localization of the Arp2/3 complex to promote dynamic nuclear actin polymerization that is essential for proper virion processing and infectivity. Given the conservation of p78/83 among lepidopteran NPVs (*13*, *17*), it is likely that these viruses use the same mechanism for nuclear actin polymerization. It seems quite possible that other unrelated pathogens have also evolved similar strategies for exploiting nuclear actin (*18*). Because pathogens rarely invent cell biological processes, preferring to adapt existing pathways to their own needs, we suggest that AcMNPV may have co-opted existing nuclear functions and regulatory mechanisms of actin to facilitate its replication.

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19. We thank R. Tsien and J. Thorner for the mCherry construct, M. Roe for *T. ni* ARPC3/p21 expressed sequence tags, G. Blissard and O. Lung for materials for recombinant bacmid generation, J. Vlak for plasmid pCRcass1, L. Guarino for plasmid *Eco*RI-I/pUC7 and pp31 antibody, M. Goldberg and K. Gunsalus for cofilin antibody, J. Washburn for determining WOBpos virus virulence in insects, R. Jeng and C. Haglund for preparing dsRNA, S. Ruzin and D. Schichnes for microscopy assistance, R. Jeng and A. Siripala for comments on the manuscript, and the Welch and Volkman labs for helpful discussions. This work was supported by a NSF graduate fellowship (E.D.G.), federal Hatch funds (L.E.V.), NIH National Institute of Allergy and Infectious Diseases grant AI054693 (W.Z.C.), NIH National Institute of General Medical Sciences grant GM59609 (M.D.W.), and grants 2004-35607-14906 (M.D.W.) and 2002-35302-1260 (L.E.V.) from the National Research Initiative of the U.S. Department of Agriculture Cooperative State Research Education Extension Services (CSREES).

Supporting Online Material

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Movies S1 to S5

2 August 2006; accepted 11 September 2006
10.1126/science.1133348

S6K1- and βTRCP-Mediated Degradation of PDCD4 Promotes Protein Translation and Cell Growth

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The tumor suppressor programmed cell death protein 4 (PDCD4) inhibits the translation initiation factor eIF4A, an RNA helicase that catalyzes the unwinding of secondary structure at the 5′ untranslated region (5′UTR) of messenger RNAs (mRNAs). In response to mitogens, PDCD4 was rapidly phosphorylated on Ser^{67} by the protein kinase S6K1 and subsequently degraded via the ubiquitin ligase $SCF^{\beta TRCP}$. Expression in cultured cells of a stable PDCD4 mutant that is unable to bind βTRCP inhibited translation of an mRNA with a structured 5′UTR, resulted in smaller cell size, and slowed down cell cycle progression. We propose that regulated degradation of PDCD4 in response to mitogens allows efficient protein synthesis and consequently cell growth.

The proteolysis of many cellular regulators is controlled by SCF (SKP1–CUL1–F-box protein) ubiquitin ligases (*1*). In humans, there are 68 SCF ligases (*2*), each characterized by a different F-box protein subunit that provides specificity by directly recruiting the substrate. Mammals express two distinct paralogs of the F-box protein βTRCP (βTRCP1 and βTRCP2), with biochemical properties that are indistinguishable. We will therefore use the term βTRCP to refer to both, unless specified.

To identify new substrates of the $SCF^{\beta TRCP}$ ubiquitin ligase, we used an immunopurification strategy that enriches for ubiquitylated substrates, followed by mass spectrometry analysis (*3*). In addition to peptides derived from known

$SCF^{\beta TRCP}$ substrates, we also recovered three peptides corresponding to programmed cell death protein 4 (PDCD4), not previously identified as an $SCF^{\beta TRCP}$ substrate.

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PDCD4 is a tumor suppressor protein that is lost in certain aggressive human carcinomas and whose expression inhibits transformation in cultured cells and in a mouse model of tumorigenesis [reviewed in (*4*) and (*5*)]. PDCD4 binds the eukaryotic translation initiation factor (eIF) 4A (*6*–*8*), an RNA helicase that catalyzes the unwinding of mRNA secondary structure at the 5′ untranslated region (5′UTR). PDCD4 also binds eIF4G (*7*, *9*) and is thought to prevent translation by competing with eIF4G for binding to eIF4A, or inhibiting eIF4A's helicase activity, or both.

Because protein translation is stimulated by mitogens, we examined their impact on the abundance of PDCD4. Human T98G cells (revertants from T98 glioblastoma cells that acquired the property to accumulate in G_0/G_1 in low serum) and normal human fibroblasts were deprived of serum for 72 hours and then reactivated by addition of serum. In mitogen-deprived cells, the overall amount of PDCD4 increased, but after mitogen stimulation, it rapidly decreased (Fig. 1A and fig. S1). Treatment of the cells with the proteasome inhibitor MG132 prevented the disappearance of PDCD4 (Fig. 1B).

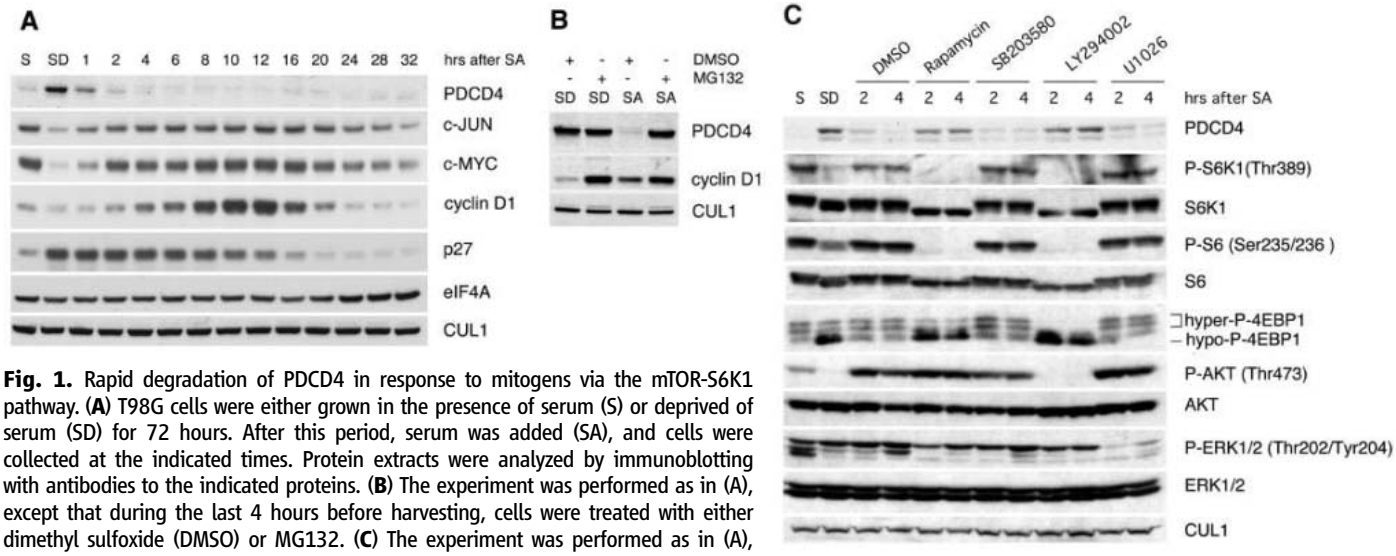


Fig. 1. Rapid degradation of PDCD4 in response to mitogens via the mTOR-S6K1 pathway. (**A**) T98G cells were either grown in the presence of serum (S) or deprived of serum (SD) for 72 hours. After this period, serum was added (SA), and cells were collected at the indicated times. Protein extracts were analyzed by immunoblotting with antibodies to the indicated proteins. (**B**) The experiment was performed as in (A), except that during the last 4 hours before harvesting, cells were treated with either dimethyl sulfoxide (DMSO) or MG132. (**C**) The experiment was performed as in (A), except that, together with serum, various drugs were added, as indicated.

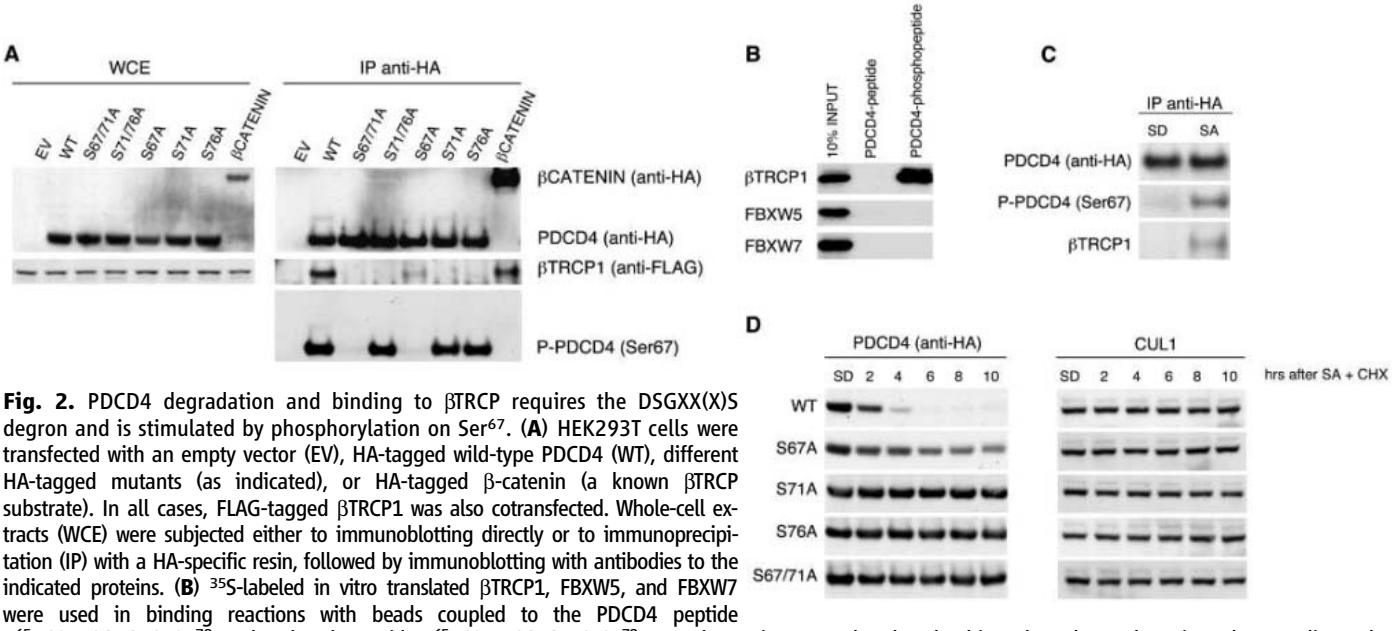


Fig. 2. PDCD4 degradation and binding to βTRCP requires the DSGXX(X)S degron and is stimulated by phosphorylation on Ser^{67}. (**A**) HEK293T cells were transfected with an empty vector (EV), HA-tagged wild-type PDCD4 (WT), different HA-tagged mutants (as indicated), or HA-tagged β-catenin (a known βTRCP substrate). In all cases, FLAG-tagged βTRCP1 was also cotransfected. Whole-cell extracts (WCE) were subjected either to immunoblotting directly or to immunoprecipitation (IP) with a HA-specific resin, followed by immunoblotting with antibodies to the indicated proteins. (**B**) ^{35}S-labeled in vitro translated βTRCP1, FBXW5, and FBXW7 were used in binding reactions with beads coupled to the PDCD4 peptide K^{65}NSSRDSGRGDSVSD^{79} or the phosphopeptide K^{65}NSSRDpSGRGDpSVSD^{79}. Bound proteins were eluted and subjected to electrophoresis and autoradiography. (**C**) T98G cells infected with a retrovirus expressing HA-tagged PDCD4 were deprived of serum (SD) for 72 hours and then activated with serum for 1 hour (SA). Cells were treated with MG132 for 3 hours before harvesting and lysis, and extracts were then subjected to immunoprecipitation with a HA-specific resin (anti-HA), followed by immunoblotting with antibodies to the indicated proteins. (**D**) T98G cells were infected with a retrovirus expressing either HA-tagged wild-type PDCD4 or HA-tagged PDCD4 mutants, as indicated. After serum deprivation (SD) for 72 hours, cells were activated with serum (SA) for the indicated times in the presence of cycloheximide (CHX). Cells were then collected, and proteins were analyzed by immunoblotting with an antibody against HA (left panels) to detect PDCD4 or with an antibody against CUL1 (right panels) to show normalization of the loading.

To gain insight into the pathways involved in the degradation of PDCD4, we reactivated mitogen-deprived cells with serum in the presence of various drugs. LY294002, a phosphoinositide 3-kinase (PI3K) inhibitor, prevented the proteolysis of PDCD4 (Fig. 1C). The fact that rapamycin, an inhibitor of mTOR (mammalian target of rapamycin), but not PI3K or the protein kinase AKT (which are both upstream to mTOR), had the same effect as LY294002 indicated that the mTOR-ribosomal protein S6 kinase 1 (S6K1) pathway is involved in promoting the degradation of PDCD4. The stabilization of PDCD4 paralleled (i) the lack of S6K1 phosphorylation and activation, (ii) the lack of S6 phosphorylation, and (iii) the decreased phosphorylation of 4EBP1, a known mTOR substrate. In contrast, the addition of SB203580 and U1026, inhibitors of p38 and extracellular signal–regulated kinases (ERKs), respectively, had no effect on the degradation of PDCD4.

The physical interaction between PDCD4 and βTRCP observed by mass spectrometry suggests that $SCF^{\beta TRCP}$ is the ubiquitin ligase targeting PDCD4 for degradation. This interaction is specific, because βTRCP1 and βTRCP2 were the only F-box proteins that coimmunoprecipitated with PDCD4 (fig. S2). Furthermore, PDCD4 contains a canonical βTRCP-binding motif [D^{70}SGRGDS^{76} (*10*) in human PDCD4] (fig. S3A). In all substrates investigated so far, the two serine residues in the DSGXX(X)S degron (where X represents any amino acid) must be phosphorylated to allow recognition by βTRCP (*11*). In many βTRCP substrates, phosphorylation on residues surrounding the degron promotes the phosphorylation of the two serine residues present in the degron (*1*). The putative βTRCP-binding motif in PDCD4 is immediately preceded by a Ser that is part of a canonical RXRXXS phosphorylation consensus site for S6K1 (R^{62}LRKNS^{67} in human PDCD4) (fig. S3B). We generated a number of PDCD4 mutants [all with hemagglutinin epitope (HA) tags] in which Ser^{67}, Ser^{71}, or Ser^{76} were mutated individually or in various combinations to Ala (e.g., Ser^{67} to Ala, S67A) (fig. S3C). After expression of these proteins in human embryonic kidney HEK293T cells, we immunoprecipitated them with HA-specific resin. Although wild-type PDCD4 immunoprecipitated efficiently with βTRCP1, the PDCD4(S71A), PDCD4(S76A), and PDCD4(S71/76A) mutants did not (Fig. 2A). This suggests that Ser^{71} and Ser^{76} may be phosphorylated in vivo and may mediate the binding to βTRCP. Accordingly, a peptide (amino acids 65 to 79) from PDCD4 containing both phosphorylated Ser^{71} and Ser^{76} efficiently bound βTRCP1 (but not FBXW5 and FBXW7), but a corresponding nonphosphorylated peptide did not (Fig. 2B).

Compared with the wild-type protein, PDCD4(S67A) displayed a markedly reduced binding (Fig. 2A). To investigate whether Ser^{67} is phosphorylated in cells, we used a phospho-specific antibody that recognizes the S6K1 phospho-consensus motif RXRXXpS (*12*). This antibody recognized wild-type PDCD4 but not PDCD4(S67A) or PDCD4(S67/71A) (Fig. 2A). Notably, PDCD4 appeared to be phosphorylated on Ser^{67} and associated with βTRCP1 in activated cells but not in serum-deprived cells (Fig. 2C).

Compared with wild-type PDCD4, the half-lives of PDCD4 mutants were increased in ac-

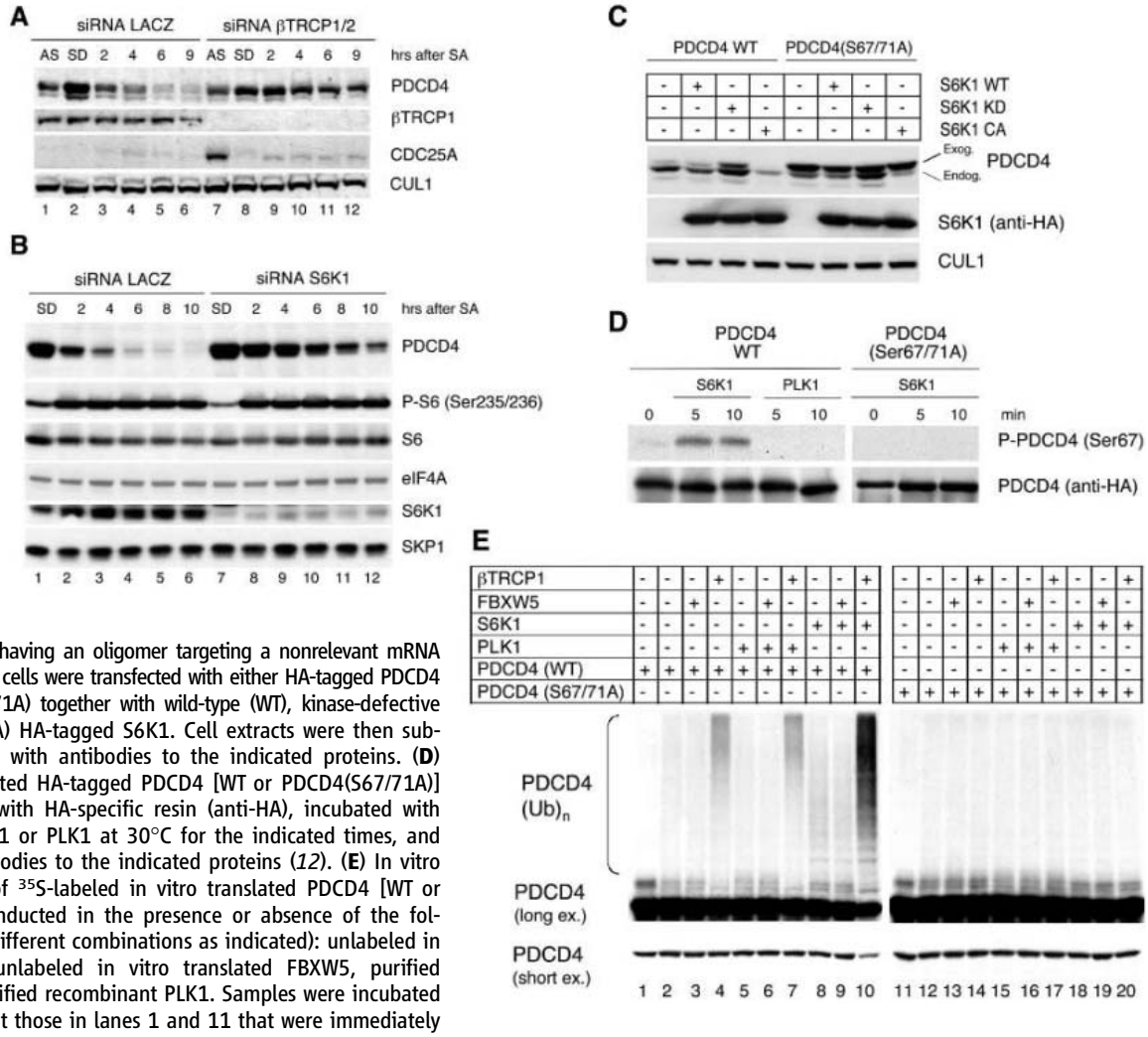


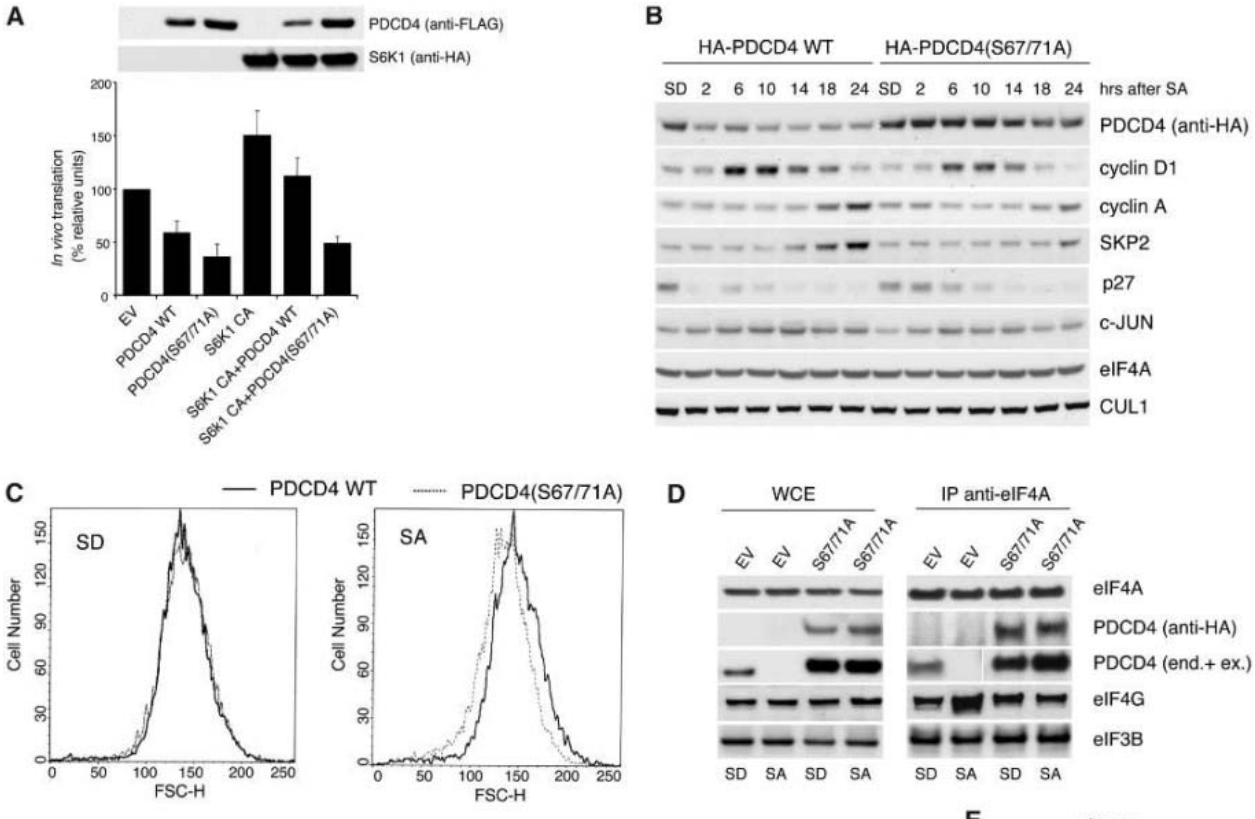
Fig. 3. Control of ubiquitylation and degradation of PDCD4 by βTRCP and S6K1. (**A**) T98G cells were transfected twice with siRNA molecules to a nonrelevant mRNA (LacZ) or to both βTRCP1 and βTRCP2 mRNA. Cells were deprived of serum (SD) for 36 hours and then activated with serum (SA) for the indicated hours. Lanes 1 and 7 show extracts from asynchronously growing cells (AS). Protein extracts were probed with antibodies to the indicated proteins. (**B**) The experiment was performed as in (A), except that effects with a dsRNA oligo to S6K1 (lanes 7 to 12) were compared with those having an oligomer targeting a nonrelevant mRNA (lanes 1 to 6). (**C**) HEK293T cells were transfected with either HA-tagged PDCD4 or HA-tagged PDCD4(S67/71A) together with wild-type (WT), kinase-defective T229A (KD), or T389E (CA) HA-tagged S6K1. Cell extracts were then subjected to immunoblotting with antibodies to the indicated proteins. (**D**) Unlabeled in vitro translated HA-tagged PDCD4 [WT or PDCD4(S67/71A)] was immunoprecipitated with HA-specific resin (anti-HA), incubated with purified recombinant S6K1 or PLK1 at 30°C for the indicated times, and immunoblotted with antibodies to the indicated proteins (*12*). (**E**) In vitro ubiquitin ligation assay of ^{35}S-labeled in vitro translated PDCD4 [WT or PDCD4(S67/71A)] was conducted in the presence or absence of the following proteins (used in different combinations as indicated): unlabeled in vitro translated βTRCP, unlabeled in vitro translated FBXW5, purified recombinant S6K1, or purified recombinant PLK1. Samples were incubated at 30°C for 90 min, except those in lanes 1 and 11 that were immediately added to sample buffer. The bracket on the left side of the top panels marks a ladder of bands corresponding to polyubiquitylated PDCD4.

tivated T98G cells (Fig. 2D) and correlated with their decreased binding to βTRCP (Fig. 2A). To further test whether βTRCP might regulate the stability of PDCD4, we used small interfering RNA (siRNA) to reduce the expression of βTRCP in T98G cells. We used a double-stranded RNA (dsRNA) oligomer that efficiently targets both βTRCP1 and βTRCP2 (*3*). Depletion of βTRCP inhibited the degradation of PDCD4 after serum addition (Fig. 3A).

Because Ser^{67} is part of a canonical phosphorylation site for S6K1 and because rapamycin and LY294002 inhibit PDCD4 degradation, we tested whether S6K1 might promote the βTRCP-mediated proteolysis of PDCD4. Inhibition of expression of S6K1 in cultured cells with a dsRNA oligomer (*13*) inhibited the phosphorylation (fig. S4) and degradation (Fig. 3B) of PDCD4. We also examined the effects of forced S6K1 expression on PDCD4 stability in HEK293 cells (Fig. 3C). Expression of wild-type S6K1 slightly reduced the amounts of endogenous and exogenous PDCD4, whereas the constitutively active (CA) S6K1 mutant (T389E) had a stronger effect. A kinase-defective (KD) S6K1 mutant (T229A) increased the abundance of PDCD4. Overexpression of wild-type S6K1 or S6K1 mutants had no effect on PDCD4(S67/71A) abundance, further corroborating the importance of these two residues in PDCD4 stability. The phosphorylation of PDCD4 on Ser^{67} by S6K1 was confirmed in a kinase assay using purified proteins (Fig. 3D). We propose that, in response to mitogens, S6K1 is activated and phosphorylates PDCD4 on Ser^{67}. This event, in turn, promotes the phosphorylation of Ser^{71} and Ser^{76} (by S6K1 or another kinase) and allows binding to βTRCP.

We reconstituted the ubiquitylation of PDCD4 in vitro. Wild-type PDCD4, but not the PDCD4(S67/71A) mutant, was efficiently ubiquitylated only when both βTRCP1 and S6K1 were present in the reaction mix (Fig. 3E and fig. S5). A different F-box protein, FBXW5, or a different kinase, PLK1, were unable to trigger the ubiquitylation of PDCD4 (Fig. 3E).

PDCD4 inhibits the cap-dependent translation of a luciferase mRNA with a stem-loop structured 5′UTR (pCMV-SL-LUC) more effi-



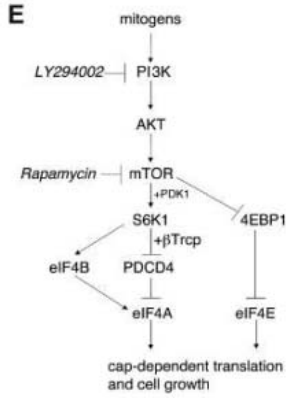


Fig. 4. Requirement of PDCD4 degradation for efficient protein translation, cell growth, and cell cycle progression. (**A**) T98G cells were transfected with the pCMV-SL-LUC reporter plasmid together with a pRL-null *Renilla* luciferase plasmid (for normalization) and constructs for the indicated proteins. Cells were allowed to recover for 18 hours and then were serum starved. Twenty-four hours later, cells were restimulated with serum for an additional 20 hours. Luciferase activities were measured by a dual-luciferase assay, and the luciferase/renilla light-unit ratio was calculated. The value of the sample transfected with an empty vector (EV) was set at 100%. Data are presented as the means ± SEM of three independent experiments (in triplicate). Amounts of exogenously expressed proteins (analyzed by immunoblotting with the indicated antibodies) are shown in the upper panels. (**B**) T98G cells were infected with a retrovirus expressing green fluorescent protein (GFP) and HA-tagged wild-type PDCD4 or HA-tagged PDCD4(S67/71A). Cells expressing low levels of PDCD4 (only about three times endogenous PDCD4) were isolated by fluorescence-activated cell sorting (FACS) (using GFP as a marker). After 72 hours of serum deprivation (SD), cells were activated with serum (SA) for the indicated times. Cells were harvested and analyzed by immunoblotting. (**C**) A representative experiment performed as in (B). Cell size was determined by FACS (forward scatter) in cells deprived of serum (SD) and 12 hours after serum addition (SA). (**D**) The experiment was performed as in (B). Four hours after serum addition (SA), whole-cell extracts (WCE) were either subjected directly to immunoblotting or to immunoprecipitation (IP) with an antibody against eIF4A, followed by immunoblotting with antibodies to the indicated proteins. (**E**) Model of how βTRCP and S6K1 control protein translation and cell size by promoting the degradation of PDCD4. For general reviews about protein translation, see references (*14*–*16*).

ciently than a nonstructured luciferase reporter (*8*). To study the biological significance of PDCD4 proteolysis, PDCD4 (wild-type or the S67/71A mutant) and CA S6K1 expression plasmids, as well as the pCMV-SL-LUC plasmid, were transiently transfected into T98G cells in various combinations, and then luciferase activities were measured (Fig. 4A). PDCD4(S67/71A) inhibited translation more efficiently than wild-type PDCD4, in agreement with its higher expression level after serum addition. Accordingly, silencing of βTRCP inhibited luciferase activity (fig. S6). In contrast, expression of CA S6K1 increased translation (Fig. 4A). Whereas wild-type PDCD4 poorly counteracted the effect of CA S6K1, expression of PDCD4(S67/71A) completely neutralized the stimulation by CA S6K1. All together, these results show that the regulated degradation of PDCD4 positively modulates protein translation in vivo.

We also infected T98G cells with retroviruses expressing HA-tagged wild-type PDCD4 or HA-tagged PDCD4(S67/71A). Cells were deprived of serum for 72 hours and then restimulated for various times (Fig. 4B). Expression of PDCD4(S67/71A) induced a slower accumulation of cyclin D1, cyclin A, and SKP2, and a slower degradation of p27. Thus, expression of PDCD4(S67/71A) delays the G_1-to-S phase transition of the cell cycle. Because S6K1 regulates cell growth (*14*, *15*), we measured cell size by flow cytometry. After serum stimulation, cells expressing PDCD4(S67/71A) displayed decreased cell size relative to cells expressing wild-type PDCD4 (Fig. 4C).

Finally, we investigated how the presence of larger amounts of PDCD4 influences the binding between eIF4A and eIF4G. In response to serum, when PDCD4 was degraded, the association between eIF4A and eIF4G increased more than twofold (Fig. 4D). However, in cells expressing PDCD4(S67/71A), this increase was no longer evident, correlating with the observed >50% inhibition of translation (Fig. 4A).

We propose that the degradation of PDCD4 in mitogen-stimulated cells is necessary for efficient protein translation, which is a prerequisite for cell growth and, consequently, cell proliferation (*16*, *17*) (Fig. 4E). Moreover, our findings implicate S6K1 and $SCF^{\beta TRCP}$ in the regulation of PDCD4 degradation and highlight the importance of the ubiquitin system in the control of translation initiation in response to mitogens.

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10. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; Y, Tyr; and X, any amino acid.
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18. We thank T. Bashir, S. Biffo, M. Benet, T. Cardozo, S. Fumagalli, I. Mohr, T. Ohta, and D. Ruggero for suggestions and/or critically reading the manuscript and O. Afonja, J. Blenis, M. Chao, I. Mohr, R. Schneider, and E. Skolnik for reagents. M.P. is grateful to T. M. Thor for continuous support. N.V.D. is grateful to G. Sirico and V. Dorrello. This work was supported by American Italian Cancer Foundation fellowships to N.V.D. and A.P., an Emerald Foundation grant to D.G., and grants from the NIH (R01-CA76584 and R01-GM57587) to M.P.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5798/467/DC1
Materials and Methods
Figs. S1 to S6
References

22 May 2006; accepted 9 August 2006
10.1126/science.1130276

Functional Delivery of a Cytosolic tRNA into Mutant Mitochondria of Human Cells

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Many maternally inherited and incurable neuromyopathies are caused by mutations in mitochondrial (mt) transfer RNA (tRNA) genes. Kinetoplastid protozoa, including *Leishmania*, have evolved specialized systems for importing nucleus-encoded tRNAs into mitochondria. We found that the *Leishmania* RNA import complex (RIC) could enter human cells by a caveolin-1–dependent pathway, where it induced import of endogenous cytosolic tRNAs, including $tRNA^{Lys}$, and restored mitochondrial function in a cybrid harboring a mutant mt $tRNA^{Lys}$ (*MT-TK*) gene. The use of protein complexes to modulate mitochondrial function may help in the management of such genetic disorders.

The A8344G mutation (A to G nucleotide mutation at position 8344) in the *MT-TK* gene in myoclonic epilepsy with ragged red fibers (MERFF) (*1*) causes a substantial reduction in the rate of translation of most mitochondrial mRNAs, as well as the accumulation of aberrant translation products (*2*), which results from inefficient aminoacylation of (*3*) and/or codon recognition by (*4*) the mutant tRNA. More severe defects are observed in patients possessing deletions of this gene: for example, in Kearns-Sayre syndrome (KSS), a 1.9-kb mitochondrial deletion covers the *MT-TK* gene, as well as the neighboring *CO2*, *CO3*, *ATP6*, and *ATP8* genes (*5*). Cytoplasmic hybrids (cybrids), derived from such patients and carrying mutant mitochondria, are good in vitro models for monitoring the efficacy of correctional protocols. Partial rescue of mitochondrial function in cybrids, and in primary fibroblasts from MERRF patients, by transfection of variants of yeast $tRNA^{Lys}$ genes has been reported (*6*), but this approach suffers from low efficiency, variability, and toxicity of the transfection vehicle.

The RNA import complex (RIC), isolated from the inner membrane of *Leishmania* mitochondria, is a large (M_r ~ 600 kD) multisubunit aggregate containing several tRNA binding proteins (fig. S1 and table S2) that is active for specific, adenosine triphosphate (ATP)–dependent translocation of tRNAs (*7*, *11*). Human cytoplasmic $tRNA^{Lys}$(UUU) is imported into the mitochondria of transgenic *Trypanosoma brucei* (*8*) and transiently transfected *L. tropica* (*9*), as well as into isolated *Leishmania* mitochondria (*9*). Moreover, purified RIC induces import of the same tRNA into human mitochondria in vitro (*10*). The imported tRNA undergoes multiple rounds of lysylation within the organelle and directly donates lysine to the translating ribosome, correcting the translational defects in MERRF-derived mutant mitochondria (*10*). We tested the hypothesis that RIC can be used to induce functional tRNA import in whole cells.

To monitor uptake of RIC, we incubated monolayer cultures of either the human hepatocarcinoma (Hep) G2 cell line or cybrids containing wild-type (LB58), MERRF patient–derived (LB64), or KSS (FLP32.39) mitochondria with affinity-purified fluorescent-tagged RIC (*11*), and live cells were imaged at various

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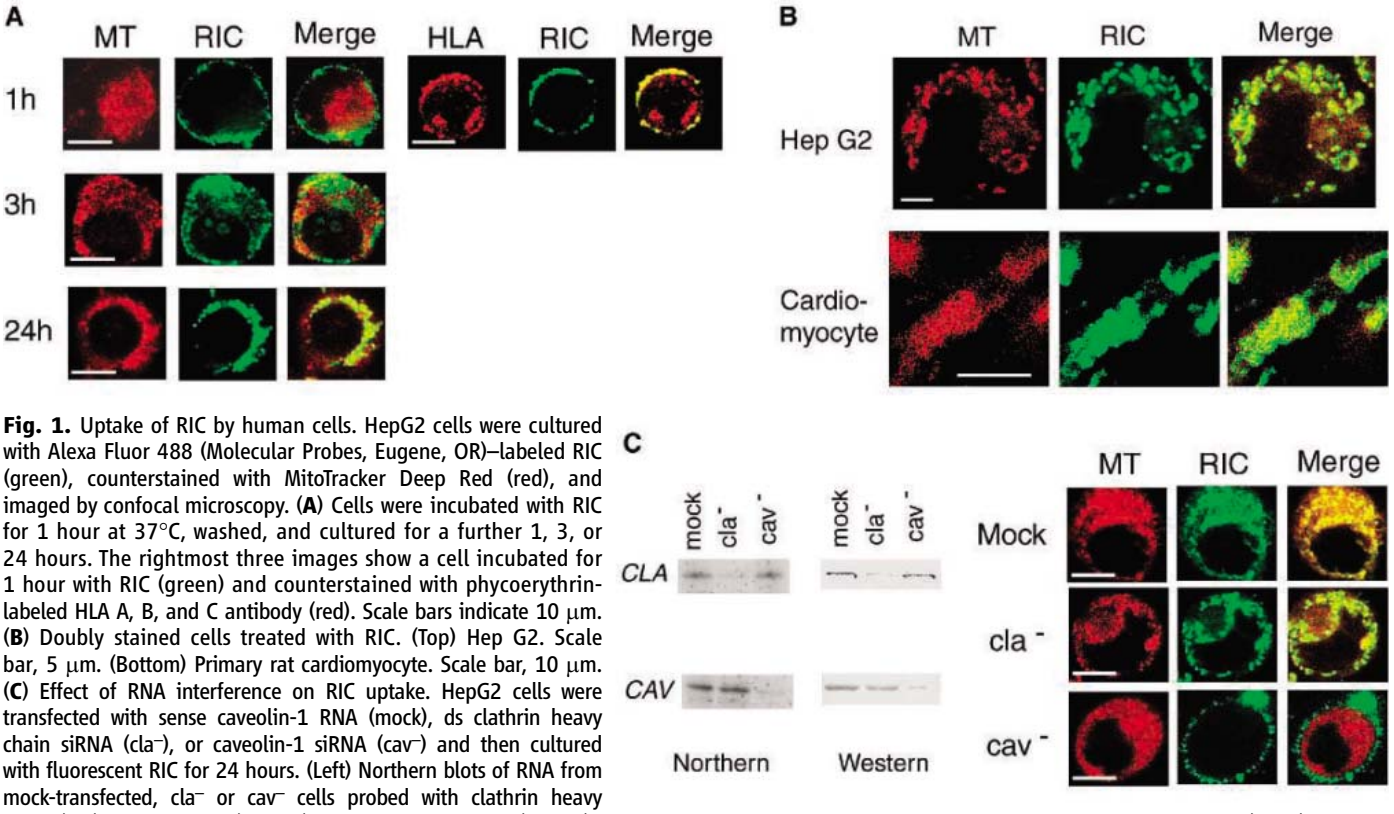

Fig. 1. Uptake of RIC by human cells. HepG2 cells were cultured with Alexa Fluor 488 (Molecular Probes, Eugene, OR)–labeled RIC (green), counterstained with MitoTracker Deep Red (red), and imaged by confocal microscopy. (**A**) Cells were incubated with RIC for 1 hour at 37°C, washed, and cultured for a further 1, 3, or 24 hours. The rightmost three images show a cell incubated for 1 hour with RIC (green) and counterstained with phycoerythrin-labeled HLA A, B, and C antibody (red). Scale bars indicate 10 μm. (**B**) Doubly stained cells treated with RIC. (Top) Hep G2. Scale bar, 5 μm. (Bottom) Primary rat cardiomyocyte. Scale bar, 10 μm. (**C**) Effect of RNA interference on RIC uptake. HepG2 cells were transfected with sense caveolin-1 RNA (mock), ds clathrin heavy chain siRNA (cla⁻), or caveolin-1 siRNA (cav⁻) and then cultured with fluorescent RIC for 24 hours. (Left) Northern blots of RNA from mock-transfected, cla⁻ or cav⁻ cells probed with clathrin heavy chain (top) or caveolin-1 (bottom) antisense RNA probe. (Middle) Western blots probed with caveolin-1 or clathrin heavy chain antibody. (Right) Live cells stained as above. Scale bar, 10 μm.

times. After 1 hour, the complex was detected as discrete spots near or on the plasma membrane, as indicated by colocalization with class I histocompatibility antigen (Fig. 1A). Entry into the cytoplasm was apparent by ~3 hours, although substantial amounts were still plasma membrane–bound, and was complete by 24 hours; little or no staining was evident in the nucleus or on the plasma membrane. Counterstaining with MitoTracker Deep Red 633 (Molecular Probes, Eugene, OR), which is selectively taken up by actively respiring mitochondria (*12*), showed clear colocalization of the complex with mitochondria in more than 80% of cells (Fig. 1, A and B). The remaining cells were singly labeled, i.e., were either metabolically inactive and did not concentrate MitoTracker in their mitochondria or did not take up the complex. In addition to the human Hep G2 and osteosarcoma-derived cybrid cell lines, uptake and mitochondrial targeting of RIC were also observed in primary rat cardiomyocytes (Fig. 1B and fig. S2), indicating the presence of a pathway that is not specific for cell type.

Internalization of large particles such as viruses commonly occurs by one of two mechanisms of receptor-mediated endocytosis, involving clathrin and caveolin, respectively (*13*–*15*). To determine whether the apparent uptake of RIC is dependent on one of the established cellular endocytic pathways, we transfected cells with double-stranded (ds) small interfering (si) RNA targeted to either caveolin-1 or clathrin heavy chain mRNA, then incubated them with fluorescent-tagged RIC. In control cells transfected with caveolin-1 sense oligonucleotide, uptake and mitochondrial targeting of the complex were normal (Fig. 1C). Down-regulation of clathrin had no appreciable effect on uptake or mitochondrial localization of RIC. In contrast, 77% of caveolin-1–deficient cells were unable to take up RIC even after 24 hours; the complex remained restricted to the plasma membrane (Fig. 1C). Thus, the uptake of the complex may occur by a caveolin-1–dependent endocytotic pathway (*14*), through caveosomes, and subsequently via transport vesicles fusing with the mitochondrial membrane.

To monitor the effect of RIC on tRNA import, we examined cytosolic and mitochondrial fractions of the treated cells for the presence of cytoplasmic $tRNA^{Lys}$(UUU) by reverse transcription polymerase chain reaction (RT-PCR). In untreated cells, $tRNA^{Lys}$ was detected exclusively in the cytosolic fraction and was ribonuclease (RNase) sensitive, as expected (Fig. 2A). In contrast, the same tRNA was detected in the mitochondria of wild-type, MERFF, and KSS cybrids incubated with RIC for as little as 17 hours and was RNase resistant (Fig. 2A). About 5% of the total cytoplasmic $tRNA^{Lys}$ was recovered from the mitochondrial fraction. Titration of RIC indicated the presence of a threshold concentration (~25 ng/ml) below which no import was detectable (Fig. 2B). Thus, in the presence of exogenous RIC, cytoplasmic $tRNA^{Lys}$ was transferred into the mitochondria of intact cells.

Cycloheximide-resistant protein synthesis was assayed in mitochondria from RIC-treated cells. In mitochondria from untreated MERRF cells, there was a general reduction in the synthesis of organelle-encoded proteins; at the level of individual polypeptides, the effect varied, with some, such as ND5 and ND6, particularly sensitive and others, such as ND4L, less affected (Fig. 2E), as previously reported (*2*, *10*). These partial effects presumably reflect incomplete loss of activity [e.g., aminoacylation (*3*)] of the tRNA due to the point mutation. Moreover, aberrant translation products (M1 and M2) were observed, probably the result of premature termination by ribosomes paused at lysine codons. Within 24 hours of RIC treatment, the protein synthesis profile was restored nearly to that of wild-type , and the aberrant products were suppressed (Fig. 2E). In untreated KSS cells, there was a severe depression of all proteins except ND4L (which does not contain any lysine residues). Treatment with RIC resulted in full restoration of all proteins except COII, COIII, A6, and A8, the genes for which had been deleted (Fig. 2E).

The effect of RIC on respiratory function was checked by staining cells for cytochrome oxidase (COX, complex IV) activity. In control

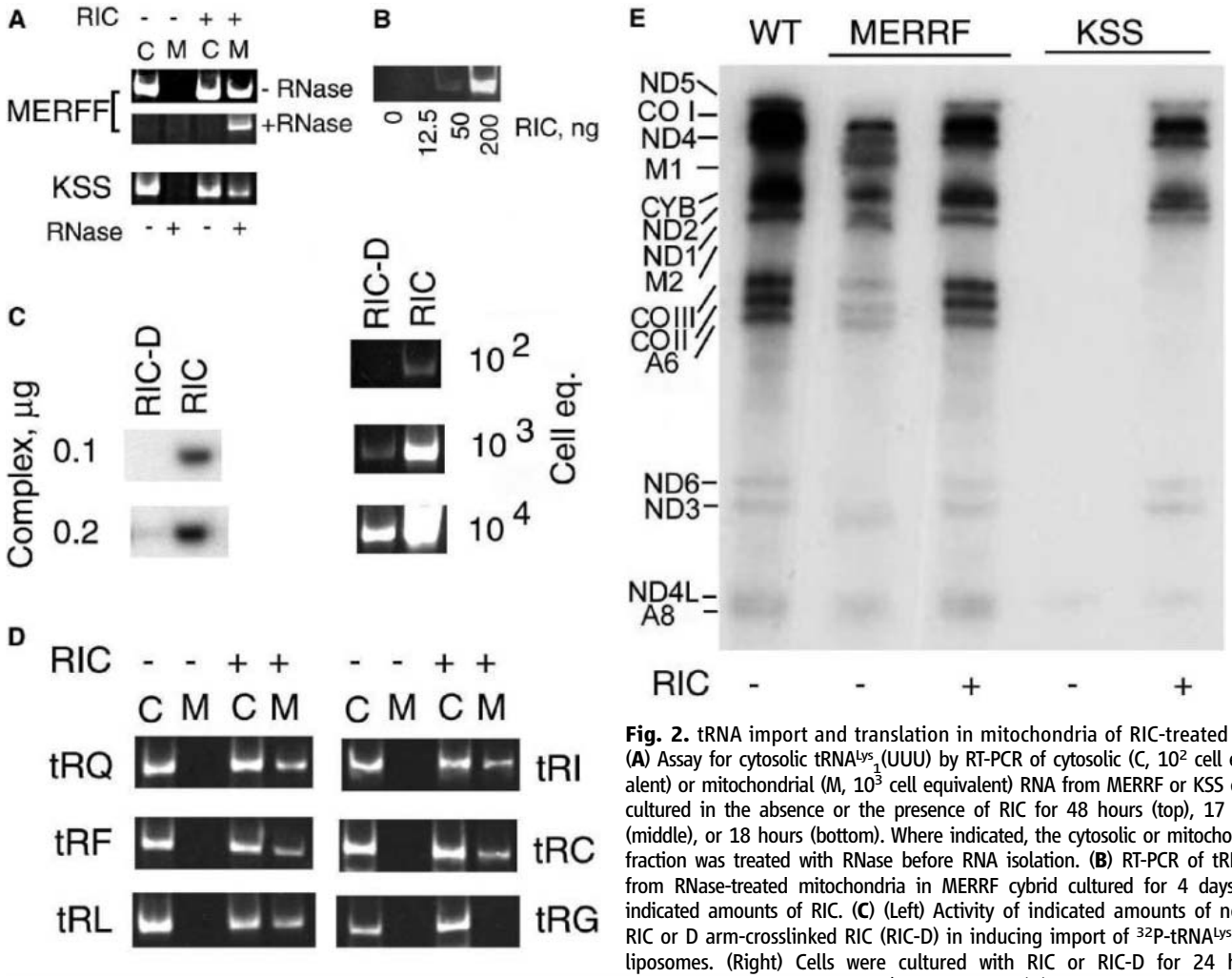

Fig. 2. tRNA import and translation in mitochondria of RIC-treated cells. (**A**) Assay for cytosolic $tRNA^{Lys}_1$(UUU) by RT-PCR of cytosolic (C, 10^2 cell equivalent) or mitochondrial (M, 10^3 cell equivalent) RNA from MERRF or KSS cybrid cultured in the absence or the presence of RIC for 48 hours (top), 17 hours (middle), or 18 hours (bottom). Where indicated, the cytosolic or mitochondrial fraction was treated with RNase before RNA isolation. (**B**) RT-PCR of $tRNA^{Lys}_1$ from RNase-treated mitochondria in MERRF cybrid cultured for 4 days with indicated amounts of RIC. (**C**) (Left) Activity of indicated amounts of normal RIC or D arm-crosslinked RIC (RIC-D) in inducing import of ^{32}P-$tRNA^{Lys}_1$ into liposomes. (Right) Cells were cultured with RIC or RIC-D for 24 hours, mitochondria were RNase treated, and indicated cell equivalents of mitochondrial RNA were assayed for $tRNA^{Lys}_1$ by RT-PCR. (**D**) RT-PCR of indicated tRNAs from cytosolic (C) or mitochondrial (M) RNA from untreated or RIC-treated MERRF cells: tRQ, $tRNA^{Gln}$(UUG); tRF, $tRNA^{Phe}$(GAA); tRL, $tRNA^{Leu}$(CAA); tRI, $tRNA^{Ile}$(GAU); tRC, $tRNA^{Cys}$(GCA); and tRG, $tRNA^{Gly}$(UCC). (**E**) Protein synthesis in mitochondria from LB58 (wild type, WT), LB64 (MERRF), or FLP32.39 (KSS) cells cultured for 48 hours in the absence or presence of RIC. Cycloheximide (100 µg/ml) was present in all reactions.

MERRF cells, COX activity was practically undetectable (Fig. 3A). Upon incubation with RIC, the number of COX-positive cells increased between days 2 and 4 to a maximum of about 80% and remained steady thereafter (Fig. 3, A and B). Maximum activity was observed at an RIC concentration of ~0.1 µg/ml, with a pronounced threshold (Fig. 3C), as observed for import (Fig. 2B). RIC had no effect on the COX activity (Fig. 3A) or other respiratory functions of KSS-derived cybrids, due to the deletion of the *CO2* and *CO3* genes (*5*). Second, live cells were stained with rhodamine 123, a fluorescent cationic lipophilic dye that is selectively taken up by actively respiring mitochondria maintaining an inner membrane potential ($\Delta\Psi$, negative inside) caused by proton translocation coupled to electron transport (*16*). Normal cells fluoresced strongly because of the mitochondrial uptake of this dye, but untreated MERFF cells showed only a low, background amount of uniform cytoplasmic staining (Fig. 3E). Treatment with RIC resulted in strong punctuate cytoplasmic fluorescence in MERRF mitochondria (Fig. 3E); the cytoplasm appeared enlarged, but this could be a secondary cytotoxic effect of accumulation of a high concentration of the dye (*16*). The mean fluorescence intensity per cell was stimulated threefold and was greater than the wild-type value, reflecting an RIC-induced increase of $\Delta\Psi$ (Fig. 3F). Oxygen uptake by MERFF cells increased between 2 and 4 days after treatment (Fig. 3G). Growth of the cells in standard media was not affected by RIC (mean generation times of 26.6, 27.3, and 26.9 hours, respectively, for normal, MERFF, and RIC-treated MERFF), and cells remained viable. In contrast, MERFF cells were unable to grow on media containing galactose in place of glucose as the carbon source (Fig. 3H), a characteristic of respiration-negative cells growing glycolytically (*17*). In the presence of RIC, growth of MERRF cells in galactose was stimulated to about 75% of the wild-type rate (Fig. 3H), indicating restoration of oxidative phosphorylation. The cytotoxicity of RIC was checked by staining treated Hep G2 cells with propidium iodide (PI, an indicator of necrosis) and annexin V (an apoptotic marker), followed by fluorescence-activated cell sorting (FACS) analysis. There was no significant increase in the number of PI-positive (0.44 to 0.61%) or annexin V-positive (3.88 to 4.15%) cells upon RIC treatment (Fig. 3I). Thus, toxic effects of RIC were absent under these culture conditions.

To examine whether the rescue of respiration by RIC was a consequence of its tRNA import activity, we blocked the tRNA binding site of the import receptor subunit RIC1 (*18*) by photochemically cross-linking it to an oligoribonucleotide containing the import signal in the D arm of *Leishmania* $tRNA^{Tyr}$ (*7*). Cross-linking resulted in a markedly reduced ability of the complex to induce import of human $tRNA^{Lys}$ in vitro (Fig. 2C). The cross-linked complex was targeted normally to mitochondria (Fig. 1) but was 10 times less efficient at inducing $tRNA^{Lys}$ import (Fig. 2C). In paral-

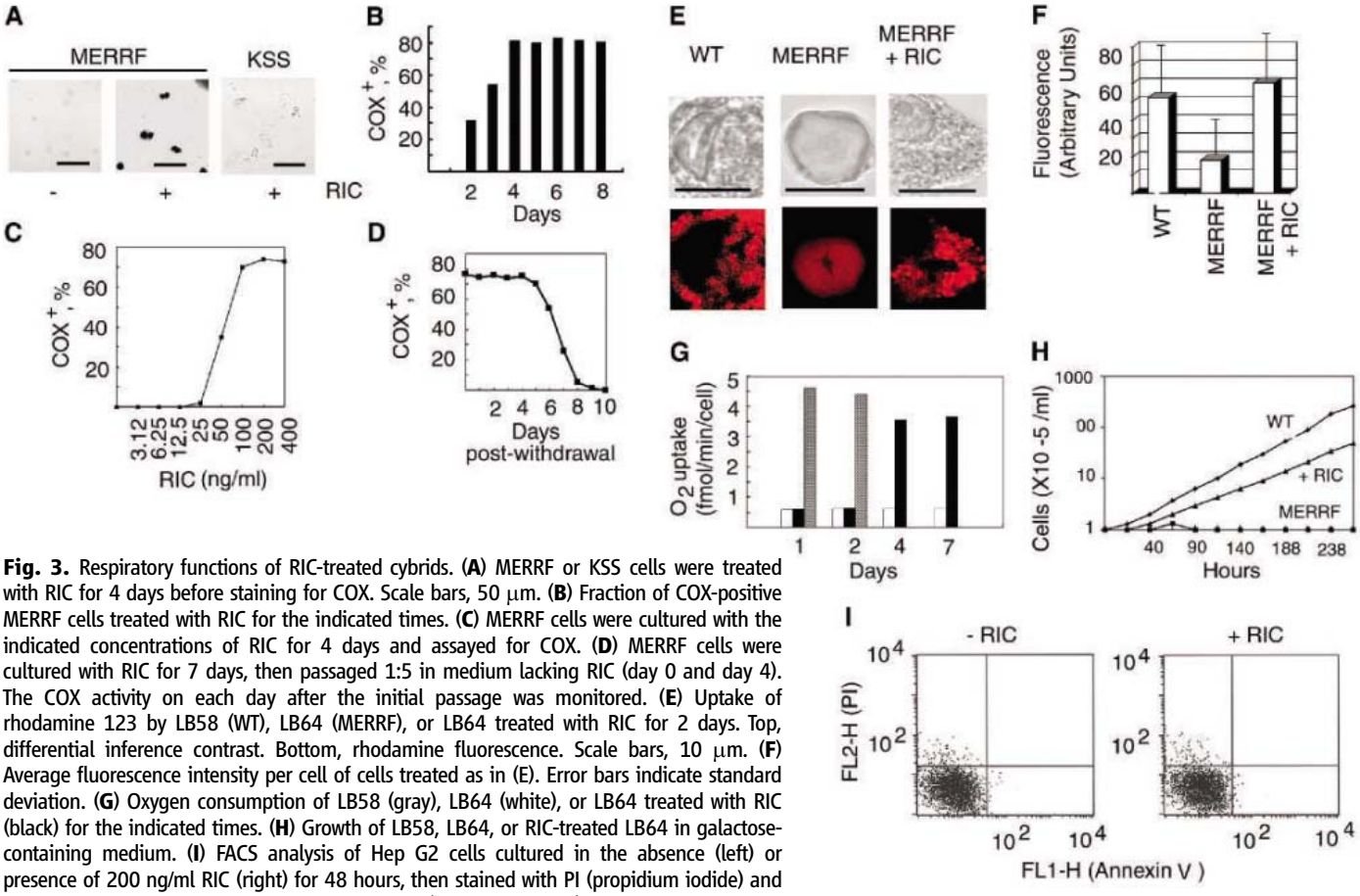

Fig. 3. Respiratory functions of RIC-treated cybrids. (**A**) MERRF or KSS cells were treated with RIC for 4 days before staining for COX. Scale bars, 50 μm. (**B**) Fraction of COX-positive MERRF cells treated with RIC for the indicated times. (**C**) MERRF cells were cultured with the indicated concentrations of RIC for 4 days and assayed for COX. (**D**) MERRF cells were cultured with RIC for 7 days, then passaged 1:5 in medium lacking RIC (day 0 and day 4). The COX activity on each day after the initial passage was monitored. (**E**) Uptake of rhodamine 123 by LB58 (WT), LB64 (MERRF), or LB64 treated with RIC for 2 days. Top, differential inference contrast. Bottom, rhodamine fluorescence. Scale bars, 10 μm. (**F**) Average fluorescence intensity per cell of cells treated as in (E). Error bars indicate standard deviation. (**G**) Oxygen consumption of LB58 (gray), LB64 (white), or LB64 treated with RIC (black) for the indicated times. (**H**) Growth of LB58, LB64, or RIC-treated LB64 in galactose-containing medium. (**I**) FACS analysis of Hep G2 cells cultured in the absence (left) or presence of 200 ng/ml RIC (right) for 48 hours, then stained with PI (propidium iodide) and fluorescein isothiocyanate–conjugated annexin V (total events, 10^4).

lel, the COX activity of MERRF cells treated with the cross-linked complex was reduced from 75 to 22%.

The stability of the RIC-induced rescue of respiration was studied as follows. MERRF cybrids were treated with RIC for 7 days then seeded into fresh media every 4 days in the absence of the complex. COX activity in these cells remained at ~75% for 5 days, subsequently declining to ~5% in another 3 days (Fig. 3D). During this period, cells grew normally, and there was no evidence of cytotoxicity. Thus, the activity was stable for over four cell generations, the subsequent fall reflecting the dilution of the pool of RIC through cycles of mitochondrial division and/or degradation of the complex.

Mitochondrial import has been observed in a wide range of organisms, but the number of tRNA species imported is highly variable, corresponding to the number of mitochondrial tRNA genes deleted or mutated, and the import mechanisms are also likely to be different (*19*). *Leishmania* mitochondria import a broad spectrum of tRNAs by a receptor-mediated process (*19*). Indeed, in addition to $tRNA^{Lys}$, a number of other cytosolic tRNAs (but not $tRNA^{Gly}$) were imported into mitochondria of human cells treated with the import complex (Fig. 2D). Thus, this approach could be applied to other disease-causing mitochondrial tRNA mutations, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MIDD (maternally inherited diabetes and deafness), caused by a mutation in mitochondrial $tRNA^{Leu}$ (*20*–*22*), or late onset Alzheimer's disease, which is associated with a mutant $tRNA^{Gln}$ (*23*, *24*). Furthermore, RIC binds to and translocates small RNAs containing import signals. This opens the possibility of introducing signal-tagged RNAs for modulating mitochondrial gene expression.

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25. We thank M. P. King for the cybrid lines, S. Bandyopadhyay for human leukocyte antigen (HLA) antibody and FACS analysis, S. Roy for annexin V, and G. Tripathi and T. Chowdhury for technical assistance. Supported by Department of Science and Technology grant nos. SR/SO/BB-28/2003 (to S.A.) and SP/SO/B50/2001 (to A.B.), Council of Scientific and Industrial Research (CSIR) project no. SMM 003, and CSIR Research fellowships to B.M., S.M., and S.M.

Supporting Online Material

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SOM Text
Figs. S1 and S2
Tables S1 and S2
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9 May 2006; accepted 6 September 2006
10.1126/science.1129754

Common *Kibra* Alleles Are Associated with Human Memory Performance

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Human memory is a polygenic trait. We performed a genome-wide screen to identify memory-related gene variants. A genomic locus encoding the brain protein KIBRA was significantly associated with memory performance in three independent, cognitively normal cohorts from Switzerland and the United States. Gene expression studies showed that *KIBRA* was expressed in memory-related brain structures. Functional magnetic resonance imaging detected *KIBRA* allele–dependent differences in hippocampal activations during memory retrieval. Evidence from these experiments suggests a role for KIBRA in human memory.

Human memory is a polygenic cognitive trait. Heritability estimates of ~50% suggest that naturally occurring genetic variability has an important impact on this fundamental brain function (*1*). Recent candidate-gene association studies have identified some genetic variations with significant impact on human memory capacity (*2*–*5*). However, the success of these studies depends upon preexisting information, which limits their potential to identify unrecognized genes and molecular pathways (*6*, *7*).

Recent advances in the development of high-density genotyping platforms now allow for high-resolution whole-genome association studies for polygenic phenotypes (*8*, *9*). We used a genome-wide screen with more than 500,000 single-nucleotide polymorphisms (SNPs). The initial screen was done in pooled DNA from a Swiss cohort that was stratified into groups of participants with different levels of episodic memory performance (verbal delayed recall). SNPs fulfilling the selection criteria of the pooling stage (*10*) were genotyped individually in this same cohort and validated in two additional cohorts from the United States and from Switzerland.

We recruited 351 young adults (median age, 22 years; range, 18 to 48 years) from Switzerland (Swiss cohort 1) (*10*). Genetic association studies in outbred populations such as this one may be prone to false positives because nonrandom genetic heterogeneity within the study sample (population structure) can lead to spurious associations between a genetic marker and a phenotype (*11*). Therefore, we controlled for genetic background and found no evidence of significant population stratification; the participants' genetic backgrounds formed one normally distributed cluster ($P = 0.6$) (*10*, *12*). We identified 10 participants as outliers (probability of cluster allocation lower than 25%) and excluded them from the genetic association studies. The remaining population ($n = 341$) was stratified into four groups according to their performance in a verbal memory task which quantified the retrieval success 5 min after learning a word list comprising 30 semantically unrelated nouns (*10*). Each of these groups was genotyped at 502,627 SNPs. To minimize the possibility of false positives (at the apparent cost of false negatives), we combined two different and stringent statistical approaches (a single-point method and, as a filter for the most significant SNPs, a sliding-window method) to select SNPs of high statistical confidence (*10*). Two SNPs fulfilled these selection criteria and were prioritized for subsequent individual genotyping to exclude pooling-related false positives: rs17070145 and rs6439886. Both SNPs map within genes expressed in the human brain: rs17070145 is a common T → C substitution within the ninth intron of *KIBRA* (GenBank accession number NM_015238), encoding a neuronal protein, and rs6439886 is a common T → C substitution within the first intron of *CLSTN2* (encoding the synaptic protein calsyntenin 2) (NM_022131).

Both the *KIBRA* and *CLSTN2* SNPs were also significantly associated with differential human memory performance when we genotyped them individually in Swiss cohort 1 using an independent genotyping technology (*10*). Carriers of *KIBRA* rs17070145 T allele had 24% better free recall performance 5 min after word presentation ($P = 0.000004$) and 19% better free recall performance 24 hours after word presentation ($P = 0.0008$) than did noncarriers (Table 1, table S1, and fig. S2). TT and CT genotype groups of rs17070145 were combined because the frequency of the TT genotype was low and because both groups displayed similar memory performance (table S1). SNP rs6439886 yielded similar results; however, the mean difference of memory performance between genotype groups was lower than that of rs17070145 (Table 1 and table S1). Both the 5-min and the 24-hour delayed free recall reflected episodic, hippocampus-dependent memory (*13*). Neither SNP was associated with performance on immediate recall tests (Table 1 and table S1), indicating that the allele-dependent differences in episodic memory were not caused by allelic effects on con-

Table 1. Association of SNPs rs17070145 (*KIBRA*) and rs6439886 (*CLSTN2*) with verbal episodic memory in Swiss cohort 1. Genotype calls of eight subjects were not considered for analysis due to low-quality pyrograms for rs17070145. Means with common superscripts are significantly different according to multifactorial analysis of variance. Data are means ± SEM.

	n	No. of words recalled		
		Immediately	After 5 min	After 24 hours
rs17070145				
CC	164	23.6 ± 0.3	7.6±0.2*	6.7 ± 0.2†
CT/TT	169	24.1 ± 0.3	9.4±0.2*	8.0 ± 0.2†
rs6439886				
TT	265	23.9 ± 0.2	8.4±0.2‡	7.3 ± 0.2§
TC/CC	76	24.2 ± 0.4	9.8±0.4‡	8.4 ± 0.4§

*$P = 0.000004$ †$P = 0.0008$ ‡$P = 0.002$ §$P = 0.022$

Table 2. Association of SNPs rs17070145 (*KIBRA*) and rs6439886 (*CLSTN2*) with episodic memory in the U.S. population. The SRT was completed by 200 participants (98 CC carriers and 102 CT and TT carriers of rs17070145). Genotype calls of seven participants were not considered for analysis because of low-quality pyrograms for rs6439886. Means with common superscripts are significantly different according to multifactorial analysis of variance. Data are means ± SEM.

	n	No. of items recalled		
		Immediately (AVLT)	After 30 min (AVLT)	Free recall task (SRT)
rs17070145				
CC	126	9.4 ± 0.3	8.5±0.3*	83.7 ± 1.2†
CT/TT	130	10.0 ± 0.3	9.7±0.3*	90.3 ± 1.1†
rs6439886				
TT	185	9.7 ± 0.2	9.1±0.2	88.4 ± 0.9
TC/CC	64	9.9 ± 0.4	9.2±0.4	88.9 ± 1.6

*$P = 0.004$ †$P = 0.00005$

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founding factors such as motivation, attention, or working memory.

Both SNPs were further evaluated in a second, independent population of 256 cognitively normal participants (median age, 55 years; range, 20 to 81 years) from the United States. The *KIBRA* SNP showed significant association with episodic memory with the same direction of effect: T allele carriers had significantly better memory scores than noncarriers in the Buschke's Selective Reminding Test (SRT) (*14*) (Table 2). Performance on another episodic memory task, the Rey Auditory Verbal Learning Test (AVLT) (*15*), was also significantly different between allele groups (Table 2). There were no allele-dependent differences in the outcome of the Wisconsin Card Sorting Test or on the Paced Auditory Serial Attention Task, suggesting that rs17070145 was not associated with executive functions, attention, or working memory in this population. As expected, the U.S. cohort displayed substantial allelic divergence. All but 18 participants reported that they were of non-Hispanic European ancestry; the 18 exceptions were of Hispanic (9), African-American (4), Native-American (3), and Asian (2) ancestry. Exclusion of these 18 individuals had no effect on the allelic association with memory performance in this sample. Genomic control analysis showed that the exclusion of these 18 participants reduced the inflation factor λ from 1.6 to 1.2, which still indicates the presence of notable genetic heterogeneity. However, inclusion of an individual's genetic background value as a covariate had no influence on the association of the *KIBRA* genotype with episodic memory performance in this sample (*10*). *CLSTN2* SNP rs6439886 failed to show significant association with episodic memory in this older population (Table 2). The lack of significance in the U.S. population for that particular SNP may be related to differences in ethnicity or to differences in mean age between the populations.

KIBRA SNP rs17070145 was further evaluated in a third population of 424 young adults (median age, 21 years; range, 18 to 28 years) from Switzerland (Swiss cohort 2), who performed a visual episodic memory task (*10*). Structured association and genomic control analysis with 122 SNPs revealed a

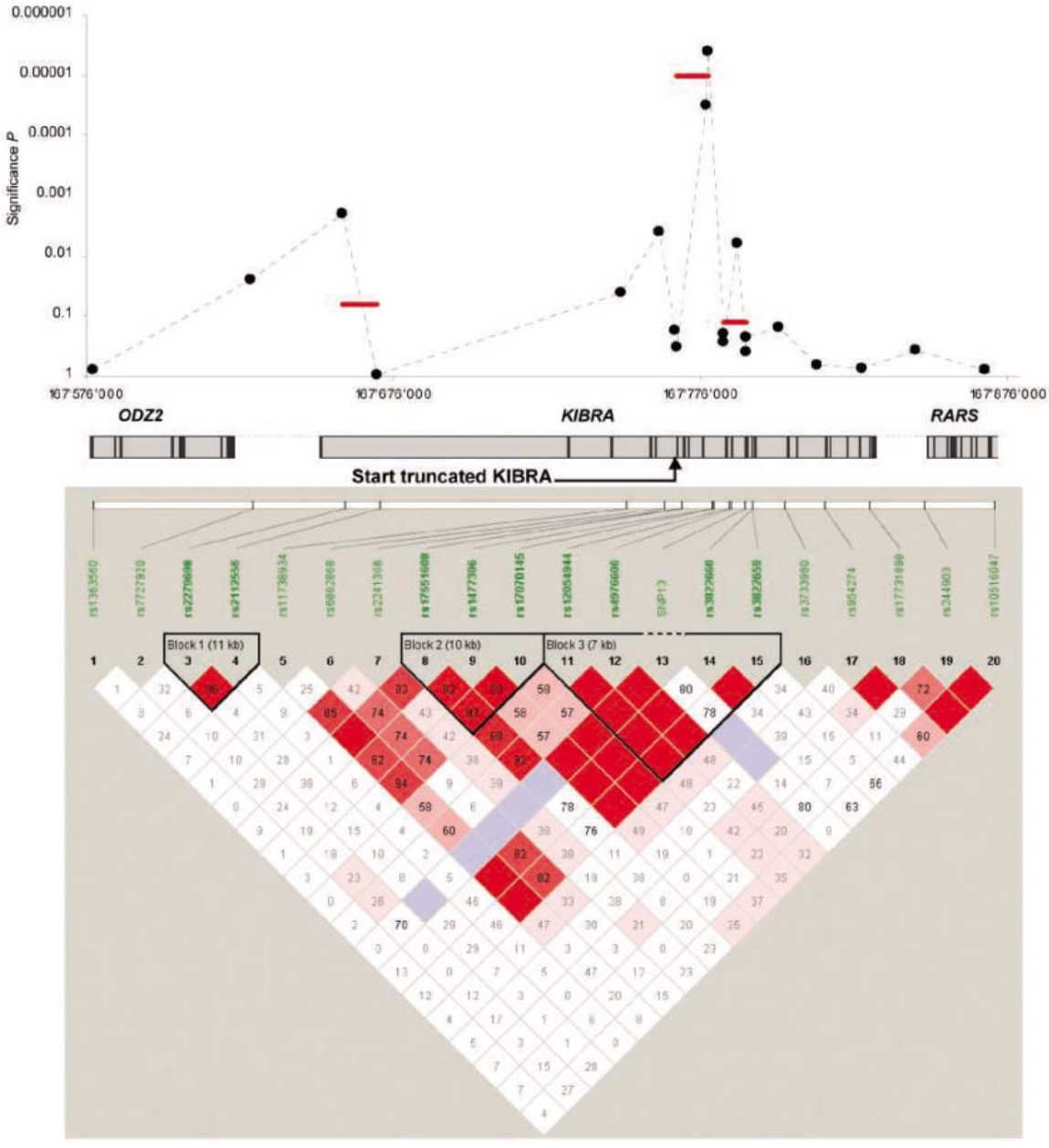

Fig. 1. Significance of SNPs and haplotypes in Swiss cohort 1. Individual genotyping in Swiss cohort 1 confirmed pooling-based screening results and implicated the *KIBRA* locus in memory performance. Black dots indicate the significance level of SNPs. Continuous red horizontal lines represent the significance level of specific haplotypes. Chromosome position in base pairs from the p terminus of chromosome 5 for each SNP is given on the *x* axis. Intronic regions of the *ODZ2*, *KIBRA*, and *RARS* genes are given in shaded gray, and short vertical lines represent the exons. The lower panel visualizes the haplotype structure of the examined region as assessed by Haploview 3.2 (*29*). Red squares represent regions of high degree of LD ($D' > 0.8$). Blue squares represent regions of high LD but for likelihood of odds (LOD) ratio.

genetically homogeneous cohort ($\lambda = 1.008$). T allele carriers also performed significantly better than did noncarriers in this population (Table 3). There were no allele-dependent differences in the outcomes of the control tasks (i.e., d2 cancellation test and the digit-span task), suggesting that rs17070145 was also not associated with attention, concentration, or working memory in this population. Taken together, we found evidence for association of the T allele of rs17070145 with better episodic memory performance in three independent study populations, whereas no significant associations were found with performance in cognitive control tasks of attention, concentration, and working memory (table S2). The allelic distribution of rs17070145 differs significantly between ethnic groups according to the National Center for Biotechnology Information database of genetic variation (dbSNP). In populations of European ancestry, the T allele is the minor one with a frequency of ~25%, as also shown in this study. In contrast, in Asian populations the T allele is most frequent (75%) and in African-American populations, the T and C alleles are almost equally frequent (54% and 46%, respectively). Therefore, it would be interesting for subsequent studies to assess *KIBRA*'s relation to memory in populations of non-European ancestry.

Fine-mapping the genomic region harboring *KIBRA* and the flanking genes *RARS* and *ODZ2* with 19 additional SNPs in Swiss cohort 1 (Fig. 1) was performed to ensure that the observed association of *KIBRA* SNP rs17070145 with episodic memory was not due to linkage disequilibrium (LD) with genetic variations in nearby genes. Three haplotype blocks were observed within *KIBRA* with this set of SNPs (Fig. 1). SNP rs17070145 and the corresponding haplotype block (block 2) yielded the highest significance levels. We concluded that the observed association is unrelated to LD with adjacent genes (Fig. 1). Further fine-mapping of 32 kilobases encompassing *KIBRA* haplotype block 2 with 58 additional SNPs refined the haplotype structure of this region and revealed the existence of additional SNPs with significance levels comparable to those of rs17070145 (fig. S1). This can be fully attributed to the tight LD between these SNPs. As part of our quality control, the most significant *KIBRA* SNPs were genotyped twice in two independent laboratories with different singleplex genotyping technologies (Pyrosequencing and Amplifluor). Genotyping scoring was done manually and in a blind manner, and the level of congruence was >99%. Because missing genotype calls may inflate test statistics (*16*), we investigated the influence of calling failures on the association results of Swiss cohort 1. In 205 individually genotyped SNPs, the average calling failure rate was 3.9% for SNP assays and 2.4% for study subjects. Neither value correlated significantly with memory performance ($P > 0.5$). Inclusion of calling failures as covariate had no influence on the association of KIBRA SNPs with memory performance.

We determined expression levels of *KIBRA* in memory-related human brain regions with reverse transcription polymerase chain reaction (RT-PCR) amplicons designed to detect both *KIBRA* full-length transcript and its truncated form *KIAA0869*, which lacks the first 223 amino acids (*17*). We also studied the protein expression of truncated KIBRA with immunocytochemistry and Western blotting in fresh frozen brain tissue (temporal lobe) from 14 individuals (fig. S5). RNA expression levels of full-length *KIBRA* in the human brain were almost undetectable. In contrast, expression levels of truncated *KIBRA* were high in all memory-related structures in the human brain, including the hippocampus and the temporal lobe (Fig. 2). Furthermore, in situ hybridization studies in mice showed that KIBRA expression is highest in the dentate gyrus and the CA1 region of the hippocampal formation (Fig. 2), two key regions for memory.

Functional magnetic resonance imaging (fMRI) was done to study the relation of the *KIBRA* genotype to human memory-related neuronal activity. Thirty participants from Swiss population 1 (15 carriers of the rs17070145 T allele versus 15 noncarriers) underwent fMRI. The allelic groups were matched for sex (5 males and 10 females in each group), education ($P = 0.7$), age ($P = 0.8$), genetic heterogeneity ($P = 0.5$), and for two polymorphisms previously shown to be related to memory performance—that is, the $His^{452} \rightarrow Tyr^{452}$ SNP of the *HTR2A* gene ($P = 0.4$) and the $Val^{66} \rightarrow Met^{66}$ SNP of the *BDNF* gene ($P = 0.5$). Furthermore, the groups were matched for 5-min delayed recall performance ($P = 1$) to avoid measuring genotype-unrelated per-

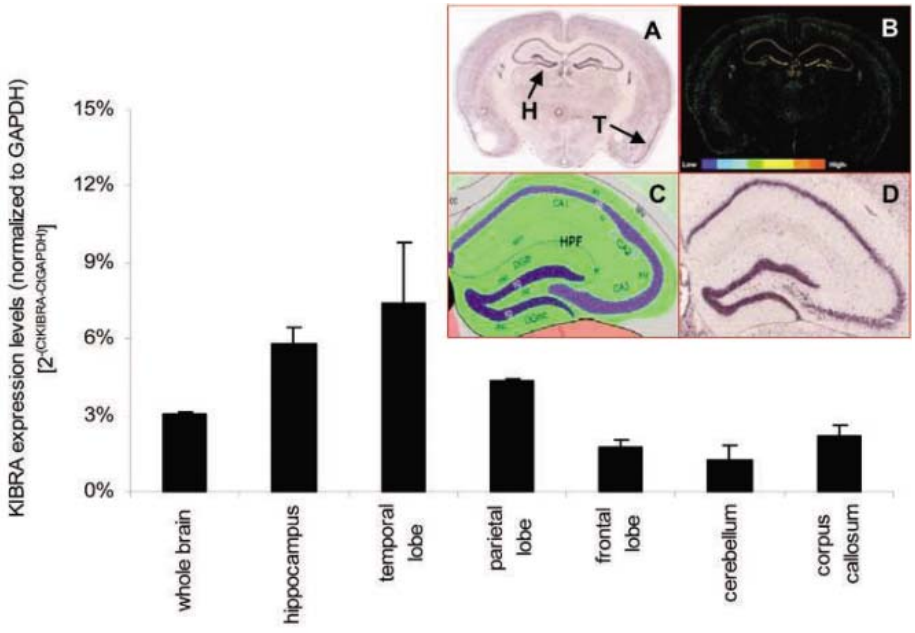

Fig. 2. KIBRA expression in memory-related structures in human and murine brain. Expression levels of truncated *KIBRA* in humans were measured by quantitative RT-PCR with data normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression levels. Error bars indicate SD. The inset shows the expression of KIBRA in the hippocampus and the temporal lobe of the murine brain as detected by in situ hybridization (*30*). Dark purple staining regions in (**A**) and (**D**) indicate areas of high KIBRA expression. (**B**) A gene expression filter with yellow and red color indicates areas of high gene expression. (**C**) An illustration of the relative atlas region. H, hippocampus; T, temporal cortex. Panels in the inset show sections scanned at high resolution (10× magnification, 0.95 μm/pixel). Panel (A) shows a coronal section of the murine brain at coronal level 72, and panel (D) is a 5× magnification of (A) showing the hippocampal formation. Data provided under license by the Allen Institute for Brain Science.

Table 3. Association of SNP rs17070145 (*KIBRA*) with visual episodic memory in Swiss cohort 2. Data are means ± SEM.

	n	Pictures recalled after 10 min	d2 test (correct characters)	Digit span (correct series)
CC	191	4.5 ± 0.1*	157 ± 2	8.9 ± 0.2
CT/TT	233	5.0 ± 0.1*	158 ± 2	8.8 ± 0.2

*$P = 0.006$

formance effects on brain activations and to instead capture genotype-dependent differences in brain-activation patterns. We expected that noncarriers of the T allele would need more activation in memory-related brain regions to reach the same level of memory performance (*18*). *KIBRA* has been associated with human episodic memory, which depends on the function of the hippocampus (*13*, *19*, *20*), leading us to also hypothesize that *KIBRA* genotypes might affect episodic memory-related information processing in the human hippocampus.

Because the hippocampus is especially activated by associative episodic memory tasks (*21*, *22*), we tested the impact of the *KIBRA* genotype on hippocampal activations in a face-profession association task. During memory retrieval, noncarriers of the T allele showed significantly increased brain activations compared with those of T allele carriers in the medial temporal lobe [local maximum in the right hippocampus at coordinate position (26,–12,–14), $t = 4.76$, $P < 0.001$, coordinates according to the Montreal Neurological Institute] (Fig. 3). Noncarriers of the T allele also showed increased activations in the frontal cortex [local maxima in the right medial frontal gyrus (Brodmann area 8/9) at coordinate position (30,42,42), $t = 4.24$, $P < 0.001$ and in the left medial frontal gyrus (Brodmann area 6) at (–24,10,56), $t = 4.38$, $P < 0.001$] and in the parietal cortex [local maximum in the right inferior parietal lobule (Brodmann area 40) at coordinate position (50,–24,30), $t = 3.97$, $P < 0.001$]. The brain regions observed in these studies belong to a network important for episodic memory retrieval (*23*), which was also activated during our memory retrieval task (fig. S3), including the medial temporal lobe [local maximum in the right hippocampus at coordinate position (32,–8,–24), $t = 4.27$, $P < 0.001$]. There was no additional increased brain activation in noncarriers of the T allele in this episodic memory task. Furthermore, in a working memory task noncarriers of the T allele failed to show any increased retrieval-related brain activation compared with that of T allele carriers, indicating that the activations in non-carriers were specific to episodic memory retrieval.

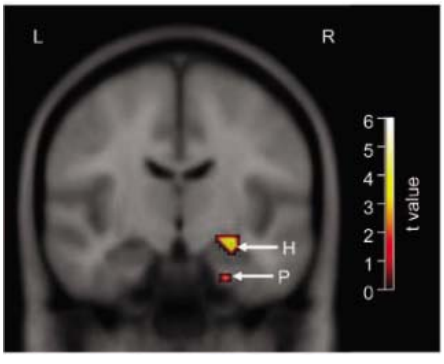

Fig. 3. Significant *KIBRA* allele–dependent differences in hippocampal activation as measured with fMRI. Activations are significantly increased in the hippocampus in noncarriers ($n = 15$) of the T allele of SNP rs17070145 than in the hippocampus of T allele carriers ($n = 15$). Activations from all 30 individuals were overlaid on a coronal section of a T1-weighted magnetic resonance image of SPM2 and displayed in color-coded t values. Threshold: $P < 0.001$. H, hippocampus; P, parahippocampal gyrus; L, left side of the brain; R, right side of the brain.

As expected based on the matching for 5-min delayed recall performance, there were also no allele-dependent differences in retrieval performance of the fMRI task ($P = 0.5$). Our findings therefore suggest that noncarriers of the T allele need more activation in these memory retrieval–related brain regions to reach the same level of retrieval performance as T allele carriers. There was no significantly increased task-related cortical activation in the T allele group as compared to noncarriers of the T allele. No allele-dependent differences in brain activations during encoding were found, suggesting that the genotype did not affect episodic memory at this early stage of memory formation. Consistent with this observation, there were no allele-dependent differences in tasks of early memory formation in the Swiss cohort 1 (i.e., immediate recall, Table 1) or in the U.S. cohort (i.e., AVLT learning trial one, $P > 0.05$). Automated voxel-based algorithms [Statistical Parametric Mapping Software package (SPM2)] (*24*) and manual volume measurements failed to reveal significant allele-dependent differences in volumes of the hippocampus or the parahippocampal gyrus, or in white and gray matter volumes, suggesting that functional imaging results were not biased by morphological differences. Furthermore, there were no significant correlations between memory measures and any of the brain volumes.

Taken together, we present evidence from independent experiments suggesting a role for *KIBRA* in human memory. KIBRA was recently identified in a yeast two-hybrid screen as the binding partner for the human isoform of dendrin, a putative modulator of synaptic plasticity (*17*). A truncated form, which was expressed in the hippocampus, lacks the first 223 amino acids and contains a C2-like domain, a glutamic acid–rich stretch, and a protein kinase C (PKC) ζ–interacting domain (*25*). PKCζ is involved in memory formation and in the consolidation of long-term potentiation (*26*, *27*). The C2-like domain of KIBRA is similar to the C2 domain of synaptotagmin, which is believed to function as the main Ca^{2+} sensor in synaptic vesicle exocytosis (*17*, *28*). The memory-associated *KIBRA* haplotype block and SNPs we describe map within the truncated KIBRA, which contains both the C2-like and the PKCζ-interacting domains.

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31. Supported by grants from the Swiss National Science Foundation (PP00B-68859 to A.P., PP00B-106708 to D.Q., and 3100-067114 to K.H.), the Helmut-Horten Stiftung (D.Q. and A.P), the Hermann-Klaus Stiftung (D.Q.), the Emily Dorothy Lageman–EMDO Stiftung (D.Q.), the Olga Mayenfisch Stiftung (A.P.), the Baugarten Stiftung (A.P.), the National Institute of Mental Health (R01MH057899 to E.M.R), the National Institute on Aging (P30AG19610 to E.M.R.), the NIH Neuroscience Blueprint (U24NS051872 to D.A.S.), the Bisgrove charitable donation (D.A.S and D.W.C.), the State of Arizona (D.A.S and E.M.R), and the Endgame UO1 grant U01-HL086528-01 (D.A.S.). We gratefully acknowledge the Allen Brain Institute for the use of their elegant murine in situ resource. We thank J. Trent, J. Lemna, and D. Locke for assistance.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5798/475/DC1
Materials and Methods
Figs. S1 to S5
Table S1
References

11 May 2006; accepted 20 September 2006
10.1126/science.1129837

Long-Term Sustainability of a High-Energy, Low-Diversity Crustal Biome

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Geochemical, microbiological, and molecular analyses of alkaline saline groundwater at 2.8 kilometers depth in Archaean metabasalt revealed a microbial biome dominated by a single phylotype affiliated with thermophilic sulfate reducers belonging to *Firmicutes*. These sulfate reducers were sustained by geologically produced sulfate and hydrogen at concentrations sufficient to maintain activities for millions of years with no apparent reliance on photosynthetically derived substrates.

Most subsurface microbial ecosystems examined to date (including subseafloor sediments, deep-sea hydrothermal vents, terrestrial sedimentary aquifers, and petroleum reservoirs) ultimately depend on sunlight. These studies have been mostly confined to depths of less than 1 km, and the ecosystems are either supported by photosynthetically produced electron donors and acceptors transported by groundwater or seawater with ages much less than a million years, or are in constant contact with oxygenated seawater migrating through the underlying fractured basaltic aquifer (*1*–*4*). Although two occurrences of autotrophic microbial communities have been reported to exist in <300-m-deep volcanic aquifers flushed with fresh meteoric water (*5*, *6*), their long-term sustainability on H_2 and isolation from photosynthetically produced substrates have not been demonstrated. Although the existence of subsurface microorganisms at depths greater than 1 km in pristine environments is well established (*7*), much is still unknown regarding the abundance, diversity, and sustainability of these microbial communities over geological time scales.

To determine the long-term sustainability of a deep terrestrial environment, we examined the microbial diversity and metabolic activity of a 3-to 4-km-deep fracture in the 2.7-billion-year-old Ventersdorp Supergroup metabasalt, in which fracture water ages of tens of millions of years (*8*), abundant abiogenic hydrocarbons (*9*), and radiolytically produced H_2 (*10*) have been reported. To characterize the indigenous microbial composition and its principal respiratory pathway, we analyzed 16*S* ribosomal DNA (rDNA) sequences, aqueous and gas geochemistry, and stable and noble gas isotopic signatures of moderately saline groundwater emanating from a fracture zone 2.825 km below the land surface (kmbls) in the Mponeng gold mine, South Africa. This high-pressure water-bearing fracture was intersected during exploratory drilling ahead of a tunnel advancing into an unmined zone ~100 m above the Ventersdorp Contact Reef (VCR) ore zone. The fracture water was initially sampled as soon as it was safe to do so (4 days after the fracture intersection), and three subsequent samples were obtained over a 54-day interval (Table 1) to monitor drilling contamination and possible changes of community structure and geochemistry as the fracture was dewatered and before being sealed by the mine's cementation team.

Fracture water samples yielded a uniform community structure dominated by a single phylotype (MP104-0916-b1) that constituted

Table 1. Geochemical and microbiological characteristics of fracture water and mining water. NA, not available; <d.l., below detection limit, which is 1 μM for O_2 and 0.5 fg ml^{-1} for archaeal DNA; Ma, million years ago.

Sample no. (number of days since intersection)	1 (4)	2 (7)	3 (15)	4 (58)	5
Sample name	MP104E65X C-091602	MP104E65X C-091902	MP104E65X C-092702	MP104E65X C-110902	MP104E65XC-SW-091602
Origin	Fracture water	Fracture water	Fracture water	Fracture water	Mining water
Water and gas flow rates (liters min^{-1}) (borehole volumes)	40/2.4 (45)	10.9/0.8 (55)	8.2/1.2 (64)	2.3/1.7 (96)	NA
pH	9.3	9.3	9.3	9.2	NA
E_h (mV)	−330	−350	−340	−263	NA
Temperature (°C)	>60	52	52	52	20
Formate (μM)‖	7.6	NA	7.1	8.9	1.4
Acetate (μM)‖	24.6	NA	22.5	35.7	5.9
Cl^- (mM)*‖	54.1	NA	71.9	84.9	0.42
Br^- (μM)‖	125	NA	177	218	3.8
SO_4^{2-} (μM)‖	529	NA	900	1860	171
HS^- (μM)†‖	NA	1390	NA	1060	NA
H_2 (μM)†‖	1940	2600	2090	3715	NA
CH_4 (μM)†‖	8580	11800	9320	16600	NA
O_2 (μM)‡‖	6	<d.l.	<d.l.	<d.l.	285
δ^2H-H_2 (‰ VSMOW)‖	−684	−684	−688	−695	NA
δ^{13}C-CH_4 (‰ PDB)§‖	−31.6	−31.7	−32.8	−33.2	NA
δ^2H-CH_4 (‰ VSMOW)‖	−364	−367	−366	−390	NA
^{4}He model age (Ma)	20.9 ± 10.5	20.4 ± 10.2	15.8 ± 7.9	NA	NA
^{40}Ar model age (Ma)	16.3 ± 8.2	21.3 ± 10.6	16.9 ± 8.4	NA	NA
^{134}Xe model age (Ma)	18.7 ± 7.0	19.4 ± 3.8	21.0 ± 6.0	NA	NA
^{136}Xe model age (Ma)	21.6 ± 6.0	25.0 ± 3.8	23.8 ± 4.6	NA	NA
Bacterial DNA (pg ml^{-1})	15 ± 8	16 ± 8	30 ± 15	30 ± 15	3 ± 1.5 × 10^5
Archaeal DNA (pg ml^{-1})	~5 × 10^{-4}	<d.l.	~5 × 10^{-4}	~5 × 10^{-4}	206 ± 100
Cell density (cells ml^{-1})	5.1 ± 0.5 × 10^4	NA	NA	3.3 ± 0.3× 10^4	NA

*The concentrations derived from charged balance were 10.2 mM for sample 1, 27.6 mM for sample 3 and 50.6 mM for sample 4. †The concentrations of dissolved gases were reported as concentrations corrected for diffusive loss (*8*). Diffusive correction was not applied to sample 4 because of the lack of noble gas analysis. ‡The positive O_2 content for sample 1 may be derived from incomplete isolation of fracture water from the mining environment caused by the extremely high water pressure and flow rate. §The carbon isotopic value was referenced to Pee Dee belemnite (PDB). ‖The uncertainties for aqueous and gas chemistry are ±10% and ±20%, respectively. The uncertainties for isotopic measurements are ±0.5‰ for δ^{13}C-hydrocarbon and ±5‰ for δ^2H-hydrocarbon and δ^2H-H_2.

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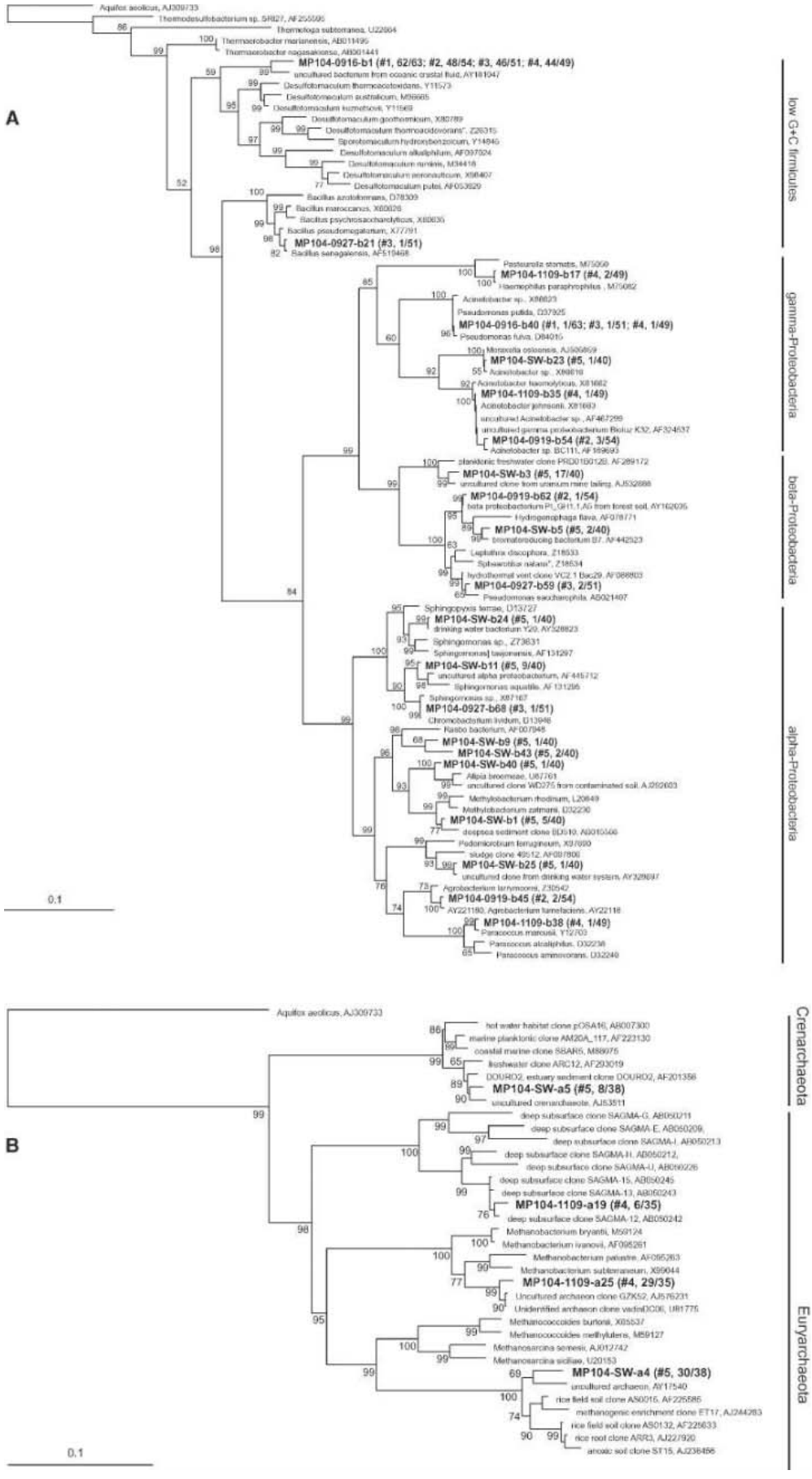

Fig. 1. Phylogenetic trees for bacteria (**A**) and archaea (**B**) based on 16*S* rDNA sequences recovered from fracture and mining water in the Mponeng gold mine, South Africa. The fraction number in parentheses represents the number of clones for each phylotype versus the total number of clones analyzed in each sample. The scale bar is equivalent to the sequence variation of 10%.

>88% of the clones in the 16*S* rDNA libraries we generated but did not appear in the water used for mining (Fig. 1A). This phylotype was related (96% similarity) to an uncultured clone recovered from thermal fluids of oceanic crust (*11*) or to *Desulfotomaculum kuznetsovii* (91% similarity) (*12*), a sulfate reducer growing at moderately thermophilic conditions. Of the other minor bacterial and archaeal phylotypes associated with the fracture water, MP104-1109-a19 resembled (98% similarity) environmental clones (the SAGMEG-2 group) obtained from fracture water in an adjacent mine (*13*) (Fig. 1B). Other phylotypes were closely related (98 to 99% similarity) to environmental clones recovered from surface environments (such as soils and sludge) or to various mesophiles distributed within *Proteobacteria*, *Firmicutes*, and *Methanobacteria* (Fig. 1). These minor phylotypes did not resemble those from the mining water [see supporting online material (SOM)].

High-density 16*S* rDNA microarray analysis was also used as a more sensitive approach to assess microbial diversity. Array hybridization results supported the finding that microbial diversity was much less (table S2) and the *Firmicutes* were of greater relative abundance (table S3) in the fracture water than in the mining water. Some overlap between the sequences found in the fracture water and those in the mining water is expected because mining water is a mixture of recycled fracture water and surface water.

The geochemistry of the fracture water was characterized to identify its origin and to assess the principal metabolic pathways (Table 1 and tables S1 and S4). Over the observation period, the temperature decreased from >60° to 52°C, while the pH was constant and the redox potential (E_h) increased from –330 to –263 mV. The Cl^-, Br^-, and SO_4^{2-} concentrations increased significantly, whereas other anion concentrations fluctuated or decreased slightly. Reduced gases (H_2 and CH_4) were abundant (>1 mM), and their concentrations increased as water flow rates declined and gas flow rates remained constant. Formate and acetate concentrations ranged from 7 to 9 μM and 22 to 36 μM, respectively. The δ^2H and $\delta^{13}C$ of the abundant dissolved C_{1-4} hydrocarbons indicated an abiogenic origin, based on their similarity to abiogenic hydrocarbon gases identified at other Precambrian Shield sites (*9*). The δ^2H and $\delta^{18}O$ values of the fracture water, –29.1 per mil (‰) and –6.9‰ VSMOW (Vienna standard mean ocean water), respectively, plotted slightly above the global and local meteoric line (*14*). The δ^2H-H_2 values ranged between –680 and –690‰ VSMOW, which when compared with the δ^2H-H_2O value yielded isotopic equilibrium temperatures of 62°C for the first sample, declining to 49°C for the last sample. Based on the thermal conductivity model (*15*) and the heat flow data (*16*), the initial temperature equates to that at 4.2 kmbls and the final temperature to that at 2.9 kmbls.

Noble gas analyses yielded elevated radiogenic and fissiogenic concentrations of ^4He, ^{40}Ar, ^{134}Xe, and ^{136}Xe (table S1) but exhibited no systematic trend during the observation period. The bulk model age of the fracture water ranged from 15.8 ± 7.9 million years to 25.0 ± 3.8 million years (Table 1). This model age represents either the true subsurface residence time or the mixing between a hydrothermal fluid that is ancient (0.8 to 2.5 billion years old); saline; and H_2-, C_{1-4} hydrocarbon–, and SO_4^{2-}-rich; and paleometeoric water that is ~3 to 4 million years old; moderately saline; and H_2-, C_{1-4} hydrocarbon– and SO_4^{2-}-poor (SOM).

The exceptional dominance of the *Firmicutes* clones; δ^2H and $\delta^{18}O$ values of the fracture water that are distinct from those of the mining water (*17*); and increasing H_2, CH_4, He, Cl^-, Br^-, and SO_4^{2-} concentrations during the observation period suggest that the fracture environment favors the survival of these *Firmicutes*-related microorganisms and that mining operations had minimal impact on this environment during depressurization and dewatering. *Desulfotomaculum*-related environmental clones and isolates have been detected in other subsurface environments, including an oil reservoir (*18*), deep sedimentary strata (*19*, *20*), an ore deposit (*21*), and saline water emanating from a 3.2-kmbls borehole located 13 km east of this borehole (*22*). The evident success of these microorganisms may not be surprising because their ability to form endospores would facilitate their survival during periods of low water activity, nutrient deprivation, and suboptimal temperature (*23*). Whether the less abundant members of the clone libraries represent indigenous microorganisms that are capable of acquiring energy through metabolisms that are distinct from those of the strains they most resemble phylogenetically, or alternatively represent moribund relics of shallower, less saline paleometeoric water that has mixed with this fracture water, is not known.

Sulfur isotopic analyses yielded $\delta^{34}S$ values of HS^- ranging from 11 to 13‰ Vienna Canon Diablo meteorite (VCDT) and those of SO_4^{2-} from 19 to 26‰ VCDT (table S4). The depleted $\delta^{34}S$ value of HS^- relative to that of SO_4^{2-} (–7.7‰ for sample 4 and –12.4‰ for sample 7) is consistent with microbial sulfate reduction. The fact that SO_4^{2-} concentrations in the fracture water were higher than that of the overlying dolomitic aquifer (*13*), and that SO_4^{2-} has been reported in analyses of fluid inclusions from hydrothermal quartz in the VCR (*24*) and the reservoir mixing-fractionation model (SOM), all suggest that the SO_4^{2-} originated from the ancient hydrothermal fluid, not the paleometeoric end member. The $\delta^{34}S$ values of fracture pyrite (0 to 2‰ VCDT) were less than that of the coexisting barite (10.1‰ VCDT) (table S4) and were consistent with those of hydrothermal 2.0-billion-year-old pyrite from the VCR in the same mine (*25*). The $\Delta^{33}S$ values for all samples clustered around 0‰ (table S4). To reproduce the $\Delta^{33}S$ of total dissolved S species (–0.022‰) for sample 7, a mixing of SO_4^{2-} derived from

Table 2. Gibbs free energy (ΔG), substrate consumption rate and steady-state free-energy flux for various microbial redox reactions.

Sample no.	1			3			4		
	ΔG (kJ mol^{-1})	Substrate rate* (μM year^{-1})	Energy flux* (kJ cell^{-1} s^{-1})	ΔG (kJ mol^{-1})	Substrate rate* (μM year^{-1})	Energy flux* (kJ cell^{-1} s^{-1})	ΔG (kJ mol^{-1})	Substrate rate* (μM year^{-1})	Energy flux* (kJ cell^{-1} s^{-1})
H_2-sulfate reduction†‡	–148	5.9×10^6	-9.2×10^{-13}	–155	8.6×10^6	-1.4×10^{-12}	–146	1.8×10^7	-2.7×10^{-12}
Acetate-sulfate reduction†‡	–86	1.9×10^5	-1.7×10^{-14}	–94	1.5×10^5	-1.5×10^{-14}	–82	2.4×10^5	-2.1×10^{-14}
H_2-methanogenesis‡	–94	2.1×10^5	-2.1×10^{-14}	–95	2.9×10^4	-2.9×10^{-15}	–93	3.8×10^5	-3.7×10^{-14}
Acetate-methanogenesis‡	–33	1.9×10^5	-6.6×10^{-15}	–34	1.5×10^5	-5.5×10^{-15}	–28	2.4×10^5	-7.1×10^{-15}
Formate-methanogenesis‡	–74	1.8×10^4	-1.4×10^{-15}	–86	1.5×10^4	-1.3×10^{-15}	–42	1.8×10^3	-8.1×10^{-17}
H_2-acetogenesis‡	–62	1.4×10^5	-9.3×10^{-15}	–61	2.0×10^4	-1.2×10^{-15}	–64	2.5×10^5	-1.7×10^{-14}

*The calculation for maximum substrate consumption rate and steady-state free-energy flux is shown in SOM. †The HS^- concentration used in the calculation for sulfate reduction for samples 1 and 3 were assumed to be 1.3 mM. The free energy for sulfate reduction only varied less than 5% when HS^- concentration was changed between 1.1 to 1.5 mM. ‡The reactions for free energy calculations were as follows: H_2-sulfate reduction: $4\ H_2 + H^+ + SO_4^{2-} \rightarrow HS^- + 4\ H_2O$; acetate-sulfate reduction: $CH_3COO^- + SO_4^{2-} \rightarrow 2\ HCO_3^- + HS^-$; H_2-methanogenesis: $4\ H_2 + H^+ + HCO_3^- \rightarrow CH_4 + 3\ H_2O$; acetate-methanogenesis: $CH_3COO^- + H_2O \rightarrow CH_4 + HCO_3^-$; formate-methanogenesis: $4\ HCOO^- + H^+ + H_2O \rightarrow CH_4 + 3\ HCO_3^-$; and H_2-acetogenesis: $4\ H_2 + H^+ + 2\ HCO_3^- \rightarrow CH_3COO^- + 4\ H_2O$. The uncertainties are ±10%.

pyrite oxidation and barite dissolution with a Rayleigh isotopic fractionation by microbial sulfate reduction was required (SOM). Such a mixture, composed of 30% SO_4^{2-} derived from the oxidation of pyrite by radiolytically produced oxidants (*10*) and 70% SO_4^{2-} derived from the dissolution of barite, produced an initial $\delta^{34}S$ value of 8.13‰ VCDT and a $\Delta^{33}S$ value of –0.0087‰ (SOM). The isotopic evolution from the initial 8.13‰ VCDT to the present observation (18.63‰ VCDT for total dissolved S species) requires a Rayleigh fractionation process in which 70% of the initial SO_4^{2-} was removed as microbially precipitated pyrite (SOM). By this model, the total HS^- formed by microbial sulfate reduction would be 4.35 mM [1.52 mM × 70%/30% + 0.80 mM HS^- (SOM)].

The Gibbs free energy for microbial redox reactions was calculated to provide additional constraints on the dominant respiratory pathway occurring in this fracture water. Sulfate reduction dominated the free-energy yields for a wide range of electron donor and acceptor combinations (Table 2). The free-energy yields for these reactions were much greater than the minimum requirement for synthesis of 1/3 of an adenosine triphosphate molecule by pumping one proton across the cell membrane (~ –20 kJ) (*26*). Among electron donors available for sulfate reduction and methanogenesis, H_2 yielded more free energy than acetate and formate, and H_2-utilizing sulfate reduction yielded the highest free energy and energy flux (Table 2), suggesting that CO_2-utilizing methanogens and acetogens cannot sustain as high a population density as sulfate reducers and therefore would be minor constituents of the community, as is observed in the clone libraries. The prominence of the free-energy flux for H_2-utilizing sulfate reduction over other metabolic reactions is consistent with the depletion of $\delta^{34}S$ values of HS^- relative to SO_4^{2-} (*27*) and the physiological characteristics inferred from the dominant phylotype.

The in situ rate of microbial sulfate reduction was estimated to range from 0.22 to 1.45 nM $year^{-1}$, or from 5.5×10^{-18} to 3.6×10^{-17} moles per cell $year^{-1}$ (assuming that all observed cells, 4×10^7 cells $liter^{-1}$, actively reduce SO_4^{2-}), based on the potential microbially produced sulfide [4.35 mM (SOM)] and fracture water residence time of ~3 or ~20 million years inferred from noble gas analysis. Such a rate is comparable to rates reported in subseafloor sediments (*28*) and to the estimated rate of radiolytic H_2 generation (*10*), but far less (4 to 5 orders of magnitude) than the maintenance energy demand of mesophilic sulfate reducers as determined in laboratory experiments (*29*) (SOM). The estimated in situ sulfate reduction rate, when combined with the experimental maintenance energy demand [48 mol (g dry weight cell)$^{-1}$ $year^{-1}$] (*29*) and assuming 20 fg per cell, would support only 200 to 1600 cells $liter^{-1}$, which is far below the observed $\sim 4 \times 10^7$ cells $liter^{-1}$. If cells were constantly growing and dying, then the experimental sulfate reducer yield of 12.2 g of dry weight cell mol^{-1} (*29*), when combined with the in situ sulfate reduction rate, would correspond to cell turnover times of 45 to 300 years. The isotopic estimate of the long-term in situ microbial activity, however, is 10^9 to 10^{10} times less than the maximum substrate consumption rate (Table 2), which would seem to indicate that as-yet-unidentified factors play a role in restraining the microbial respiration.

The hot, reducing, gaseous water emanating from a fracture at 2.8 to 4.2 kmbls harbored a microbial community dominated by a single *Firmicutes* phylotype. The *Firmicutes* probably penetrated the Mponeng fracture zone at current depths during infiltration of paleometeoric water between 3 and 25 million years ago and since then have relied on nonphotosynthetically derived H_2 and SO_4^{2-} converted from Archaean/Proterozoic pyrite/barite. Nutrient concentrations have remained much higher than observed in shallower crustal environments, suggesting that the deep crustal biosphere may be energy-rich, is not approaching entropic death, and is capable of sustaining microbial communities indefinitely by geological processes.

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30. This work was supported by grants from NSF Life in Extreme Environments and NASA to T.C.O.; the National Science Council of Taiwan to L.-H.L. and P.-L.W.; the Jet Propulsion Laboratory, NASA Cosmochemistry, and NSF Earth Science to D.R.; the Deutsche Forschungsgemeinschaft (German Research Foundation) to J.L.-P.; the NASA Indiana-Princeton-Tennessee Astrobiology Initiative to L.P.; the National Science and Engineering Research Council of Canada and Killam Fellowship funds to B.S.L.; and the U.S. Department of Energy to T.C.H. We thank J. Hall, G. Southam, G. Wagner, B. Tipple, T. Gihring, E. Van Heerden, and D. Litthauer of the Witwatersrand Microbiology Project, R. Wilson of SRK-Turgis Technology, and geologists of the Mponeng mine for their assistance in the setup of the field laboratory, field sampling, and the coordination of logistic supply. We also acknowledge D. Chivian for discussion of DNA data and S. Ono for assisting with sulfur isotope analysis. GenBank accession numbers for sequences are from DQ088779 to DQ088817.

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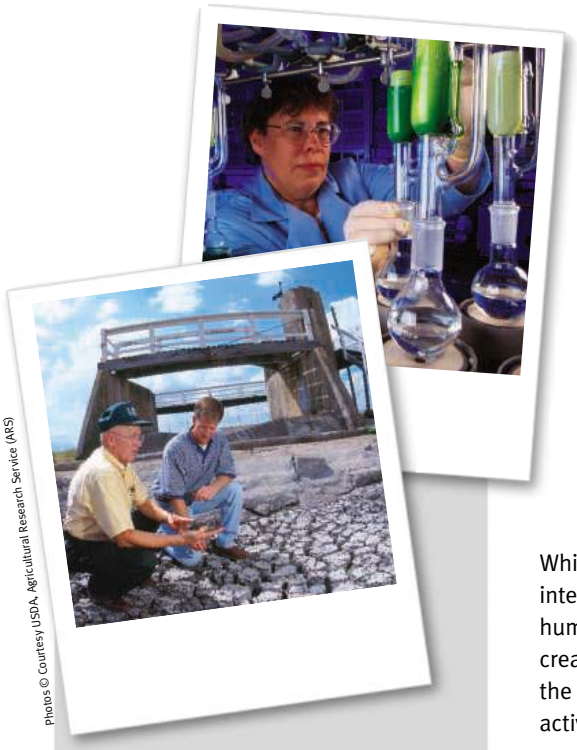

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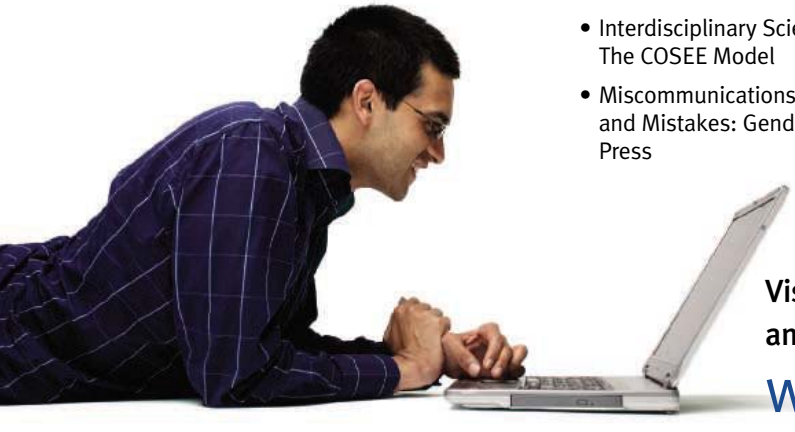

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The field of robotics involves almost every scientific discipline and will one day affect most aspects of daily life. This seminar aims to give attendees unique insights into the latest research and advances, societal implications, and future applications in this rapidly advancing field. Part 1 will delve into the many subfields of robotics, the latest innovations such as walking robots and predictive software, and moral concerns. Part 2 will cover what changes to expect and how they will affect our daily lives, including the technical, economic, and social aspects of robots being integrated into society. Robot demonstrations are planned as well as an open discussion on consumer applications that will include speakers from both parts of the seminar.

Virtual Worlds Seminar

With tens of millions of participants generating tens of billions of dollars in value, virtual worlds are powerful forces in the lives of their residents. Virtual world residents are exploring amateur-to-amateur education, creating new communities, discovering new forms of play, and leveraging rapid innovation to build new economies. Part 1 will explore virtual world communities and what they are accomplishing from the perspectives of learning and play, and will analyze the ways in which these communities can engage in public diplomacy. Part 2 will examine some of the myriad uses of virtual worlds for research and therapy ranging from stroke therapy to business innovations.

Global Health Seminar

This three-part series will highlight how science effects health-care change in areas of the world that need it most. Part 1 features scientists from the Bay Area who are working internationally to overcome challenges in health care and who are conducting research on innovative ways to prevent disease and increase access to treatment. Part 2 focuses on the relevant challenges and scientific issues that arise when implementing disease-control programs in resource-constrained settings. Part 3 places an emphasis on the social entrepreneurship and enthusiasm for corporate responsibility and how business disciplines are being applied to improve livelihoods in many different nations.

Career Workshops

Explore potential career opportunities, gain insight into labor market issues, and participate in workshops and panel discussions aimed at career enhancement. Workshops are conducted by experienced professionals.

Plenary and Topical Speakers

Keep current by attending the plenary and topical lectures given by eminent scientists and engineers.

Plenary Lectures

Photo credit: Martha Stewart.

PRESIDENT'S ADDRESS

John P. Holdren

AAAS President, and Director, The Woods Hole Research Center; Teresa and John Heinz Professor of Environmental Policy, Harvard University

Trained in aeronautics, astronautics, and plasma physics at the Massachusetts Institute of Technology and Stanford University, Dr. Holdren previously co-founded and was co-leader for 23 years of the campus-wide interdisciplinary graduate degree program in energy and resources at the University of California, Berkeley. His work has focused on causes and consequences of global environmental change, analysis of energy technologies and policies, ways to reduce the dangers from nuclear weapons and materials, and the interaction of content and process in science and technology policy.

President's Reception: Immediately following

Steven Chu

Director, Lawrence Berkeley National Laboratory

The Science and Technology of Energy

A renowned scholar and international expert in atomic physics, laser spectroscopy, biophysics, and polymer physics, Dr. Chu oversees the oldest and most varied of the U.S. Department of Energy's multi-program research laboratories. While at Stanford University, his groundbreaking work in cooling and trapping atoms by using laser light led to the Nobel Prize in Physics in 1997, an honor he shared with two colleagues. Their discoveries, focusing on the so-called "optical tweezers" laser trap, were instrumental in the study of fundamental phenomena and in measuring important physical quantities with unprecedented precision. He also helped start Bio-X, a multi-disciplinary initiative that brings together the physical and biological sciences with engineering and medicine.

Susan Solomon

Senior Scientist, National Oceanic and Atmospheric Administration

Assessing the Physical Science of Climate Change: Key Findings of IPCC (2007)

A leading atmospheric scientist at NOAA's Earth System Research Laboratory, Dr. Solomon is well known for her pioneering work in identifying the mechanism that produces the Antarctic ozone hole and for her many contributions toward the science of global environmental problems. Within the Intergovernmental Panel on Climate Change (IPCC), she is co-chair of Working Group I, which assesses the scientific basis of the climate system and climate change. The key findings of a new report, which are the subject of this lecture, will represent a comprehensive state-of-the-science through a rigorous multi-year assessment process involving more than 130 authors and more than 600 expert and government reviewers.

Topical Lectures

Michael E. Brown

Professor of Planetary Astronomy, California Institute of Technology

Planets, Dwarf Planets, and Other Ice Balls at the Edge of the Solar System

Anthony S. Fauci

Director, National Institute of Allergy and Infectious Diseases

HIV/AIDS: 25 Years and Counting

Mohammad H.A. Hassan

Executive Director, Academy of Sciences for the Developing World

International Cooperation on Science and Technology for Sustainable Well-Being

Marcia McNutt

President and CEO, Monterey Bay Aquarium Research Institute

Sustainable Resources from the Oceans: Taking Some Lessons (Good and Bad) from the Shore Side

Elinor Ostrom

Co-Director, Workshop in Political Theory and Policy Analysis, Indiana University; Founding Director, Center for the Study of Institutional Diversity, Arizona State University

Sustainable Social-Ecological Systems: An Impossibility?

Robert Sapolsky

John A. and Cynthia Fry Gunn Professor of Biological Sciences and Professor of Neurology and Neurological Sciences, Stanford University

2007 JOHN P. MCGOVERN LECTURE IN THE BEHAVIORAL SCIENCES

Stress, Health, and Coping

Kerry Sieh

Robert P. Sharp Professor of Geology, California Institute of Technology

The Intersection of Burgeoning Human Populations and Natural Hazards

Keith Wailoo

Professor of History, Rutgers University; Fellow, Center for Advanced Study in the Behavioral Sciences, Stanford, CA

2007 GEORGE SARTON AWARD LECTURE IN THE HISTORY AND PHILOSOPHY OF SCIENCE

Discipline and Disease: The Social Transformation of Cancer in the Age of Biomedicine

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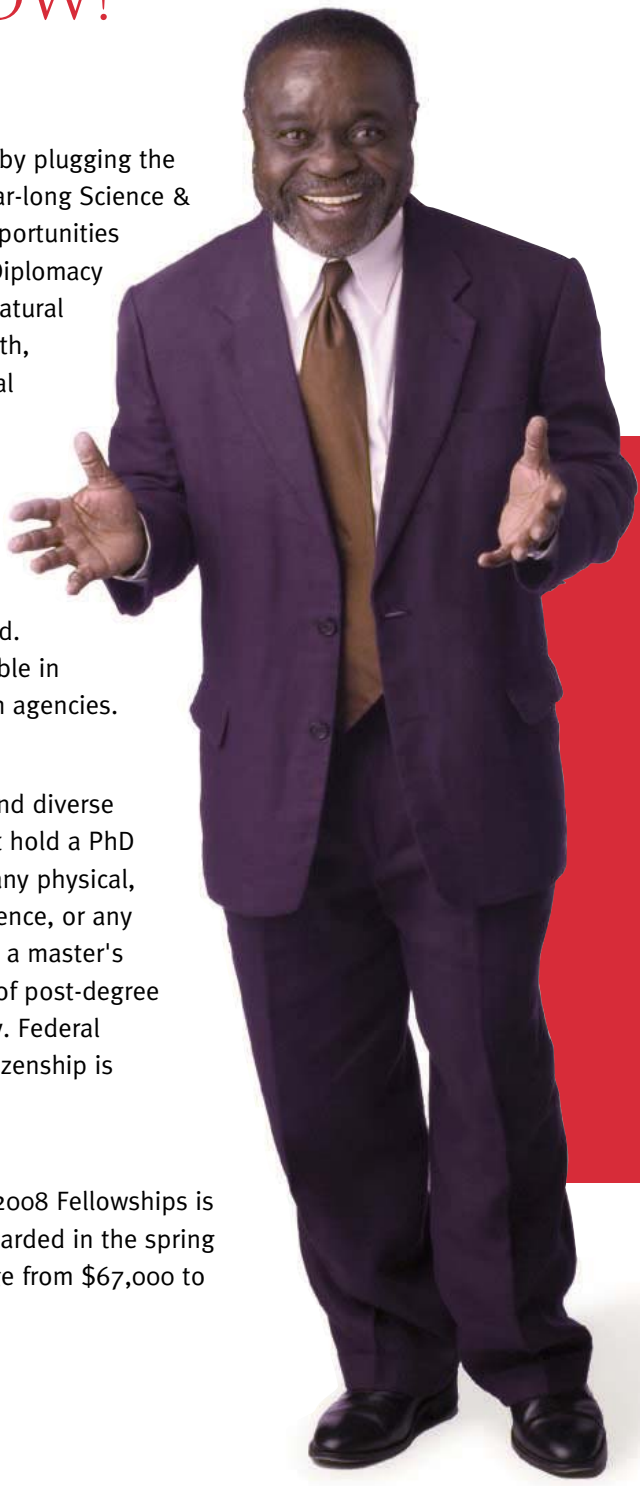

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Fred Boadu, JD, PhD

Agricultural Economics, University of Kentucky.

2005-2006 AAAS Fellow at the U.S. Department of Agriculture, Food Safety Inspection Service, Office of Policy, Program and Employee Development. Also a 1993-1994 AAAS Fellow at the U.S. Agency for International Development, Bureau for Africa/Bureau for East Asian and Pacific Affairs.

Currently associate professor and assistant head of department for undergraduate programs at Texas A & M University, which granted him a faculty development leave to complete the 2005-2006 AAAS Fellowship.

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POSITIONS OPEN

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CHAIR
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School of Medicine

Nominations or applications are invited from established, dynamic scientists with a creative vision for the position of Chair of the Department of Physiology and Biophysics at Case Western Reserve University School of Medicine.

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In addition to curriculum vitae with list of publications, applicants should submit a letter describing their research, teaching, service, administrative experience, and their vision for leading a modern Department of Physiology and Biophysics.

Review of candidates will begin immediately and continue until the position is filled. Nominations and/or applications should be e-mailed to **e-mail: chairphysiol@case.edu.**

For additional information, visit **website: http://physiology.case.edu.**

For questions or additional information you may contact **Lynn Landmesser** at **telephone: 216-368-3996** or **e-mail: lynn.landmesser@case.edu.**

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FACULTY POSITION
Microbiology/ Pathogenesis of Infectious Diseases

The Department of Microbiology at the University of Colorado School of Medicine invites applications for a tenure-eligible appointment at the level of **ASSISTANT or ASSOCIATE PROFESSOR.** Preference will be given to candidates with well-developed research expertise on mechanisms of pathogenesis of bacterial, viral, fungal, or parasitic infections. The Department of Microbiology has a research-intensive academic environment, new research and office space, a wide range of excellent core facilities, and excellent startup support. Microbiology faculty members teach medical, Ph.D. and M.D./Ph.D. students. Requirements include a Ph.D., M.D., or equivalent doctoral degree in the biomedical sciences, at least two years of post-doctoral experience within the broad field of microbiology, and a strong record of peer-reviewed publications. Associate Professor candidates should have established and productive research programs with ongoing research funding. Assistant Professor candidates should demonstrate strong productivity for their pre- and postdoctoral research, and successful competition for fellowship or career development awards is desirable. Rank and salary are commensurate with training and experience. All candidates should submit curriculum vitae, bibliography, description of research interests, list of active grants and pending grant applications, and names, mailing addresses, telephone numbers, and e-mail addresses of three professional references. Send correspondence to: **Faculty Search Committee Chair, Department of Microbiology, University of Colorado at Denver and Health Sciences Center, Mail Stop 8333, P.O. Box 6511, Aurora, CO 80045.** Review of applications will begin October 25, 2006, and continue until an appointment is made or the search is terminated. *The University of Colorado at Denver and Health Sciences Center is committed to Equal Employment Opportunity and Affirmative Action.*

POSITIONS OPEN

NEUROBIOLOGY
Keene State College

The Department of Biology at Keene State College invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level beginning fall 2007. The Department encourages applications from a diverse pool of candidates. To learn more about the School of Science and Social Science at Keene State College visit **website: http://www.keene.edu/science.**

The ideal candidate can teach a range of undergraduate courses including neurobiology and introductory biology; teach topical or interdisciplinary courses in Keene State College's new Integrative Studies Program for nonmajor students; and supervise undergraduate research. Qualifications: Require Ph.D. completed by August 1, 2007, in neurobiology or related field; a good general knowledge of biology; and some undergraduate teaching experience. Preference will be given to candidates with a strong commitment to undergraduate teaching, to liberal arts education, and to an integrated biological perspective; research experience with nonmammalian models; experience teaching integrated lecture and laboratory courses, or ability to teach cell biology, physiology, developmental biology, or anatomy. Knowledge of a specific animal group is desirable. Salary at the rank of Assistant Professor will be based on collective bargaining unit agreement, and was at $48,750 minimum in fall 2006.

For full consideration, submit letter of application, curriculum vitae, clear description of undergraduate teaching experience, statement of teaching philosophy/methods, statement of research interests, and three letters of reference (at least two addressing candidate's undergraduate teaching experience in some detail) to: **Neurobiology, FAC#20, Search Committee, Office of Human Resource Management, Keene State College, 229 Main Street, Keene, NH 03435-1604.** Review of applications will begin on December 1, 2006, and continue until position is filled.

Keene State College is a founding member of the Council of Public Liberal Arts Colleges, a national alliance of leading liberal arts colleges in the public sector. The College is accredited by the New England Association of Schools and Colleges and its education programs are National Council for Accreditation of Teacher Education-accredited. *As an Affirmative Action/ Equal Opportunity Employer, Keene State College is engaged in an effort to build a community that reflects the diversity of society.*

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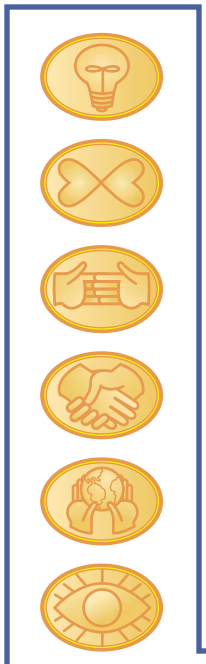
Applicants should send curriculum vitae, a statement of research and teaching interests, and three letters of recommendation to: **Professor Kenneth J. Sytsma, Chair of Search Committee, Department of Botany, University of Wisconsin, Madison, WI 53706-1381.** To ensure full consideration, applications must be received by December 12, 2006. For more information contact **e-mail: kjsytsma@wisc.edu** or consult the Department's **website http://www.botany.wisc.edu/.**

Unless confidentiality is requested in writing, information regarding the applicants must be released upon request. Finalists cannot be guaranteed confidentiality. *The University of Wisconsin is an Equal Opportunity Employer. We promote excellence through diversity and encourage all qualified individuals to apply.*



Science 2006 TOP EMPLOYER SURVEY

It All Starts with Science

This year's survey of top employers in the biotechnology and pharmaceutical industries has a familiar winner but plenty of shifting among other places in the top 20. The leading companies highlight a consistent theme: the importance of strong basic science as the platform on which to build reputations and commercial success. BY PETER GWYNNE

Showing the winning consistency of a Rocky Marciano or an Annika Sorenstam, Genentech, Inc., once more takes top place in the annual survey sponsored by *Science's* Office of Publishing and Member Services. The Northern California company has now gained the No. 1 position in each of the five years that the survey has run.

Plenty of movement has occurred among the lower placements. Boehringer Ingelheim rises to second place this year, after finishing eighth in 2005. Roche Pharmaceuticals also climbs six places, from ninth to third. GlaxoSmithKline squeezes into the top 10, after placing 11th last year. Rounding out the top 10, in fourth to ninth place, are Amgen, Inc., AstraZeneca PLC, Genzyme Corporation, Johnson & Johnson, Eli Lilly and Company, and Novartis Pharma.

The remainder of the top 20 also saw some marked changes this year. Wyeth Pharmaceuticals moves up from 19th position in 2005 to 11th in the present survey. And both Schering-Plough Corporation and Bayer make their first appearance in the top 20.

Two Key Themes

Each highly placed company has unique reasons for its success. But interviews with representatives of selected members of the top 20 reveal two key themes. Almost all the firms regard basic science as the foundation for their efforts. "We stick with what got us here – that is, having a strong focus on the science," explains Richard Scheller, executive vice president of research at Genentech.

For two other firms, increasing emphasis on science has paid dividends in terms of corporate reputation. "Our commitment to build up R&D cannot have gone unnoticed," says Roger Perlmutter, executive vice president, research and development at Amgen. "Our R&D organization has tripled in size over the past five years." Schering-Plough has a similar experience. "We set out our strategic plan for long-term high performance in 2003," says Tom Koestler, the company's executive vice president, who is also president of the Schering-Plough Research Institute. "A key component was to make investment in long-term science and technology."

Alongside top-notch science, top employers emphasize top-notch scientists. "We try to provide a working environment for our employees where they are allowed to make decisions, where they can challenge assumptions, and where they find the freedom to implement innovations," says Hans-Joachim Geppert, head of corporate division human resources at Boehringer Ingelheim. "We rely heavily on all the good people working in our organization," adds Gottlieb Keller, member of the corporate executive board and head of corporate services and human resources at F. Hoffmann-La Roche. Those "good people" also help to draw in the best and brightest recruits. Kath Yates, vice president of development and human resources at AstraZeneca, puts it best. "Talent," she says, "attracts talent."

Survey takers' feelings about the pharmaceutical, biopharma, and biotech industries also changed between last year and this. This year's respondents still note several factors that harm the industry's reputation. But they also see cause for hope in new products, therapies, and research undertaken by the industry.

One Person, One Vote

Senn-Delaney Culture Diagnostics & Measurement carried out the web-based survey between May 2 and June 4 of this year. The firm issued invitations to researchers in the United States and the European Union who were registered with AAAS or IBC Life Sciences and who identified themselves as working in biotechnology or pharmaceutical companies. All potential respondents received introductory and reminder messages via e-mail. The messages contained all necessary information about access to the survey's website. To ensure fairness, the site had a one person, one vote feature.

A total of 656 scientists participated. Almost one-third of those worked outside the United States – primarily in Western Europe. Males outnumbered females, making up 57.5 percent of the sample. Two-thirds of survey takers were at least 35 years old, and two-thirds had Ph.D., M.D., or M.D.-Ph.D. degrees.

Roughly three-quarters of respondents work in private industry, with 47 percent employed by biotechnology companies, CONTINUED »

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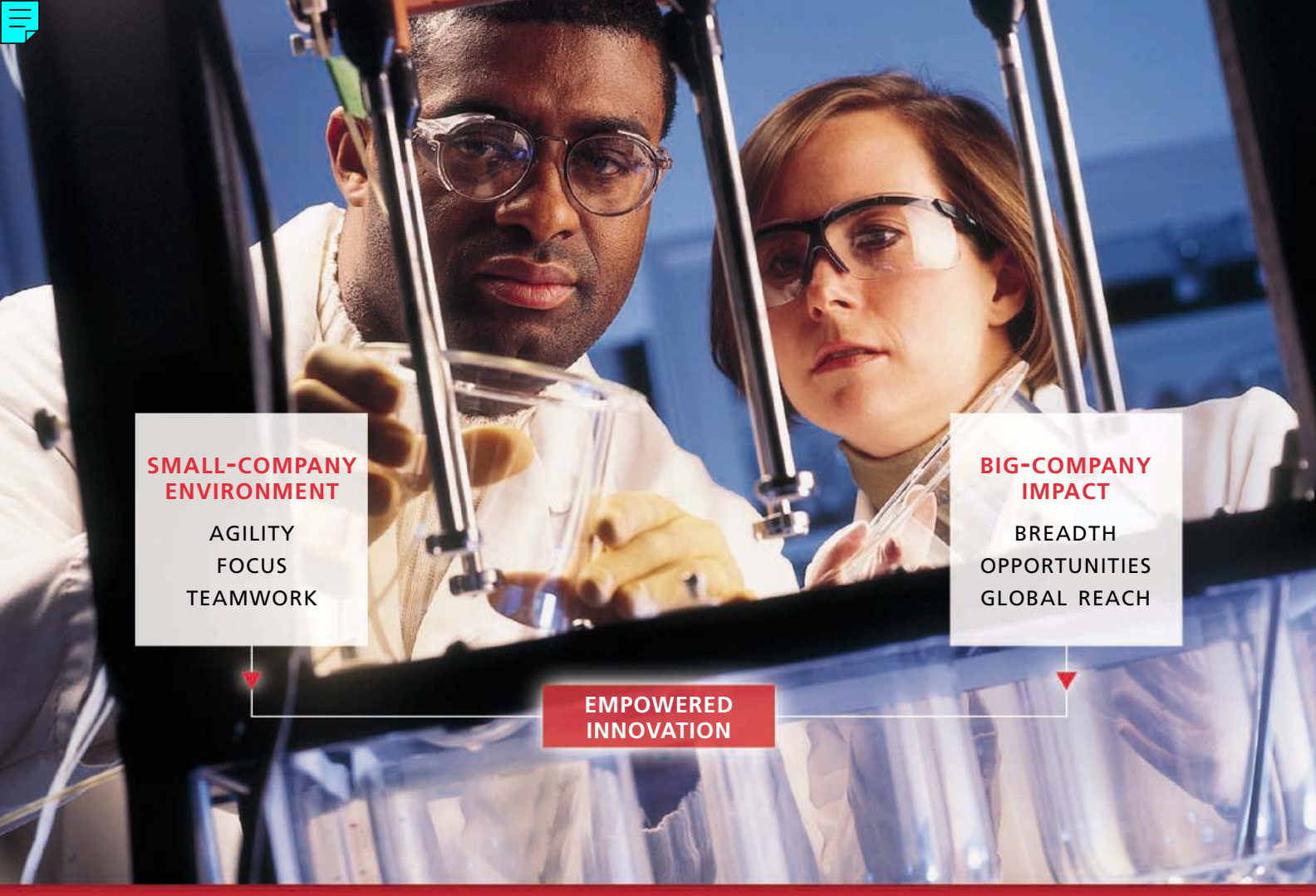

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In this role, you will develop and implement in vivo disease models for imaging and biomarker analysis in diverse animal species in all therapeutic areas. Ideal candidates will possess at least a BS degree with 8 years, or MS with 6 years of relevant research in an academic or other leading research institutions. Experience in imaging technologies (such as CT, PET, Ultrasound and MRI) is a plus. Pharmaceutical (discovery) experience desirable.

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TOP EMPLOYER SURVEY

2006 Rank	2005 Rank	Employer (Global Headquarters)	Three Top Characteristics		
1	1	Genentech, Inc. (South San Francisco, CA)	Innovative leader in the industry	Clear vision toward future	Loyal employees
2	8	Boehringer Ingelheim (Ingelheim, Germany)	Loyal employees	Innovative leader in the industry	Treats employees with respect
3	10	Roche Pharmaceuticals (Basel, Switzerland)	Innovative leader in the industry	Clear vision toward future	Work and personal values are aligned
4	2	Amgen (Thousand Oaks, California)	Innovative leader in the industry	Clear vision toward future	Loyal employees
5	4	AstraZeneca PLC (London, UK)	Socially responsible	Loyal employees	Treats employees with respect
6	6	Genzyme Corp. (Cambridge, MA)	Innovative leader in the industry	Clear vision toward future	Socially responsible
7	3	Johnson & Johnson (New Brunswick, NJ)	Socially responsible	Work and personal values are aligned	Treats employees with respect
8	7	Eli Lilly and Company (Indianapolis, IN)	Socially responsible	Innovative leader in the industry	Work and personal values are aligned
9	5	Novartis (Basel, Switzerland)	Innovative leader in the industry	Clear vision toward future	Treats employees with respect
10	11	GlaxoSmithKline (London, UK)	Innovative leader in the industry	Clear vision toward future	Loyal employees
11	19	Wyeth Pharmaceuticals (Collegeville, PA)	Innovative leader in the industry	Socially responsible	Clear vision toward future
12	12	Pfizer, Inc. (New York, NY)	Innovative leader in the industry	Clear vision toward future	Treats employees with respect
13	9	Biogen Idec (Cambridge, MA)	Innovative leader in the industry	Clear vision toward future	Treats employees with respect
14	16	sanofi–aventis (Paris, France)	Innovative leader in the industry	Work and personal values are aligned	Clear vision toward future
15	20	Serono (Geneva, Switzerland)	Innovative leader in the industry	Work and personal values are aligned	Clear vision toward future
16	14	Merck & Co., Inc. (Whitehouse Station, NJ)	Innovative leader in the industry	Clear vision toward future	Loyal employees
17	N/A[1]	Schering-Plough Corporation (Kenilworth, NJ)	Loyal employees	Innovative leader in the industry	Socially responsible
18	15	Abbott (Abbott Park, IL)	Socially responsible	Clear vision toward future	Innovative leader in the industry
19	N/A[1]	Bayer (Leverkusen, Germany)	Loyal employees	Innovative leader in the industry	Treats employees with respect
20	18	Bristol-Myers Squibb Company (New York, NY)	Clear vision toward future	Innovative leader in the industry	Loyal employees

The 20 companies with the best reputations as employers, according to respondents in the survey undertaken for the *Science* Office of Publishing and Member Services.
[1] Schering-Plough and Bayer had no ranking in 2005 because neither company received enough mentions in that year's survey.

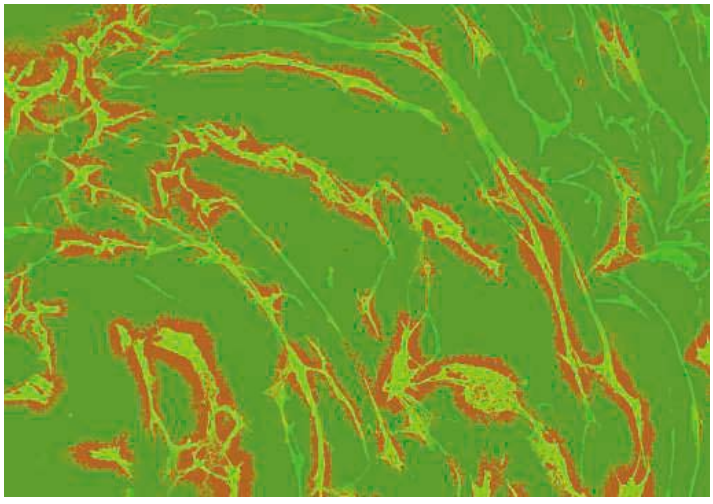
33 percent in pharmas, and the remaining 20 percent in biopharmas. Overall, 37 percent of the sample works for companies with at least 5,000 employees and 51 percent for firms that employ fewer than 1,000 individuals. While 46 percent report that they have more than 10 years of work experience, almost four out of five believe that they have not yet reached their career peak. And just under half the respondents report themselves as likely to seek a new job within the next year.

The Senn-Delaney team also asked respondents what relationship they had with the companies they chose as best. Slightly under half of the sample had a current or previous relationship with their top choice, through direct employment, consulting, or scientific collaboration.

Best, Average, and Worst

To carry out the survey, Senn-Delaney first asked respondents to choose the companies that they regarded as having the best reputations as employers in the pharmaceutical and biotechnology field, as well as those firms that they regarded as average employers and the worst employers in their experience. The survey next called on respondents to rate the companies they chose on the basis of 42 specific characteristics, such as providing job security, being a good financial investment, and being located where the individual respondent wanted to live.

Survey takers were also asked their opinions of the industry as a whole, based on events of the previous 18 months CONTINUED »



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- Bioinformatics
- Biomedical Imaging
- Cell Biology
- DMPK
- Early Leads/HTS
- Formulation
- Immunology
- Medicinal Chemistry
- Microbial Pathogenesis
- Molecular Biology
- Molecular Oncology
- Neurobiology
- Protein Chemistry
- Protein Engineering
- Translational Oncology
- Tumor Biology

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TOP EMPLOYER SURVEY

that, respondents believed, had had the greatest impact on the industry's reputation. Another question focused on the types of action that public and private institutions can take to improve the industry's reputation. Finally, the survey asked individuals to provide details about their own work and personal dynamics.

Senn-Delaney then used a mathematical process to rank each company rated in the study, based on the answers to the survey's first two items. The survey firm first identified the characteristics that most actively distinguished the best, average, and worst employers that respondents chose. Senn-Delaney then applied a statistical process that included frequency analysis, stepwise regression, and discriminant analysis. That led to a unique ranking score for each company rated. For statistical reasons, only companies that received rankings from at least 14 respondents were eligible to become part of the top 20 best employers.

Three Tiers of Companies

As in previous years, the ranking scores of the top 10 companies fitted neatly into three tiers. Last year, Genentech stood alone at the top. In this year's survey, however, Boehringer Ingelheim joins that company at the highest level, with a ranking of 90 to 100. The second tier, with scores between 80 and 89, includes, in order, Roche, Amgen, AstraZeneca, and Genzyme. And completing the top 10 in a third tier, with scores of 70 to 79, the survey identifies Johnson & Johnson, Lilly, Novartis, and GlaxoSmithKline.

The half dozen most important driving characteristics identified by respondents varied little from last year's selection. Most important, as in 2005, was "being an innovative leader in the industry." In the next place, again mirroring last year, comes "treats employees with respect." "Having work and personal values aligned," "loyal employees," and "a clear vision toward the future" once more appear in the top six driving characteristics, although in a slightly different order. And in this year's survey, "being socially responsible" replaces "does important quality research" in the leading six.

Not surprisingly, many of the top performers scored highly on the major drivers. Genentech, for example, continues to show significant advantage over the remainder of the top 10 on all six driving characteristics. Roche, in third place, has a strong showing on three drivers: innovation, values, and vision. Fourth placed Amgen also scores highly on three items: innovation, loyal employees, and vision. Further down the top 10, Johnson and Johnson and Lilly both have high scores on being socially responsible, and Novartis rates highly on vision.

Genentech's Secret

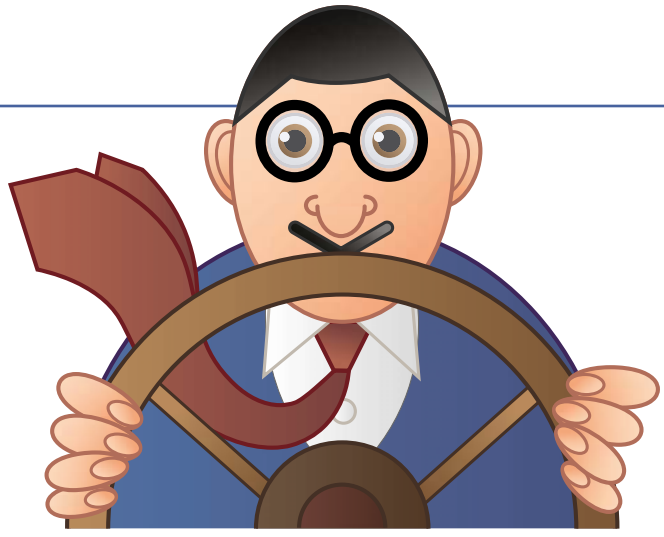
What factors continue to keep Genentech at the top of the table in the views of respondents to the survey? "I've continually thought about maintaining the balance between our basic research and our translational work, and making sure that, as the company grows and there's a need to move more molecules into the clinic, we don't lose our emphasis on basic science," Scheller explains. "One way we do that is through our large postdoctoral program. Postdocs account for about 10 percent of our scientists in research. We aim to keep them embedded in basic research. We have basic scientists next to translational scientists and embedded postdocs. The constant influx of postdocs brings new ideas, youth, and tremendous enthusiasm into the organization."

Genentech's postdocs pay off in more tangible ways. "Their goal is to make basic discoveries and to publish important research papers," Scheller notes. "This often results in our finding novel targets rather than waiting to read in the literature about the targets that others find. It would be easy, but shortsighted, not to do so much of this basic discovery work. The future is bright if it results in a translational project 10 – 15 years from now."

The company's focus on academics extends to its hiring for permanent jobs. "We rely more on academe rather than hiring from other companies," Scheller says. "We're able to attract people from academe because of our emphasis on basic discovery. We can recruit scientists from some of the best universities in the world who might not previously have thought of going into industry."

Science and Scientists

Other top performers recognize the critical importance of basic science to the mission of helping patients – and the equally important goal of attracting top-notch recruits. "Since we all share our common belief that innovation is the key to sustainable success, we do everything to foster a spirit of innovation and cross-fertilization of ideas," Boehringer Ingelheim's Geppert says. "We do this across our research and development sites, and in cooperation with academic and scientific institutions. This extends into areas of basic research, for example, through our close link with the Institute for Molecular Pathology in Vienna, Austria. Our long-term investment in this world class institution with more than 200 employees has opened invaluable opportunities for scientific exchange and cross-talk which, although CONTINUED »



Driving Characteristics of Top Employers

2005	2006
1. Innovative leader in the industry	1. Innovative leader in the industry
2. Treats employees with respect	2. Treats employees with respect
3. Clear vision toward the future	3. Work and personal values are aligned
4. Work and personal values are aligned	4. Loyal employees
5. Loyal employees	5. Socially responsible
6. Does important quality research	6. Clear vision toward the future

Colored backgrounds indicate the characteristics in common for the two years.

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APOPTOSIS
- Sr. Research Biochemist
- Biochemist/Staff Biochemist/ Research Biochemist

CARDIOVASCULAR DISEASES
- Sr. Research Biologist
  Hypertension/*In-vivo* Techniques
- Bio/Staff Bio/Research Biologist

TARGET VALIDATION
- Sr. Research Chemist
  Parallel Synthesis
- Biochemist/Staff Biochemist/ Research Biochemist

MEDICINAL CHEMISTRY
- Sr. Research Chemist/Research Fellow
  Molecular Modeling
- Chemist/Staff Chemist/Research Chemist

INFECTIOUS DISEASES
- Director, Antibacterial Drug Discovery
- Biochemist/Staff Biochemist/Research Biochemist

METABOLIC DISEASES
- Neurophysiologist/ Neuropharmacologist
  Obesity
- Bio/Staff Bio/Research Biologist

IMMUNOLOGY
- Sr. Research Immunologist
- Immunologist/Staff Immunologist/ Research Immunologist

PHARMACOLOGY
- Bio/Staff Bio/Research Biologist

West Point, PA

NEUROSCIENCE
- Sr. Research Fellow
  Alzheimer's Disease
- Sr. Research Biologists
  Sleep and Pain
- Bio/Staff Bio/Research Biologists
  In vitro/in vivo Neurochemistry, Sleep, Pain, Schizophrenia, Alzheimer's Disease, Stroke
- Bio/Staff Bio/Research Biologists
  In vivo - Alzheimer's Disease

VACCINES AND BIOLOGICS
- Sr. Research Biologist
  Molecular Virology
- Bio/Staff Bio/Research Biologists
  RNAi & Molecular Biology

CANCER RESEARCH
- Sr. Research Biologist
  RNAi

IMAGING
- Sr. Research Chemist
  Radiochemists
- Sr. Research Pharmacologists
- Bio/Staff Bio/Research Biologist - Pharmacologist
- Sr. Research Physicists
  MRI/MRS

STRUCTURAL BIOLOGY
- Sr. Research Chemist
- Bio/Staff Bio/Research Biologists

MOLECULAR ENDOCRINOLOGY
- Director
  Osteoporosis
- Sr. Research Biologist
  Sarcopenia

Boston, MA

NEUROSCIENCE
- Research Fellow
  Alzheimer's Disease
- Research Associates
  Alzheimer's Disease

MOLECULAR BIOLOGY
- Sr. Research Biologist
  Signal Transduction Pathway Analysis

DRUG METABOLISM
- Sr. Research Chemist
  In vitro and *in vivo* ADME studies
- Research Associate
  Biotransformation, Metabolite Identification and Isozyme Profiling

AUTOMATED LEAD OPTIMIZATION
- Research Fellow
- Sr. Research Biologist
  Focused Library Screening
- Sr. Research Biologist
  Physicochemical Compound Profiling/Screening
- Research Associate
  Assay Development/Lead Optimization
- Research Associate
  Tissue Culture
- Lab Robotics/Automation Software Engineer

PHARMACOLOGY
- Group Leader
  Oncology Pharmacology
- PhD Scientist
  Oncology Pharmacology
- Sr. Research Biologist
  Alzheimer's Disease/Molecular Pharmacology
- Sr. Research Biologist
  CNS Histology & Imaging
- GEMM Manager
  Oncology Pharmacology
- Research Associate
  In vivo Imaging
- Research Associate
  Behavioral Pharmacology

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The Scientific Programme of EMBL emphasises experimental analysis at multiple levels of biological organisation, from the molecule to the organism, as well as Computational Biology, Bioinformatics and Systems Biology. Within this structure, Organismal Biology occupies a critical position with strong links to our other activities. The Unit applies a wide range of modern technologies to diverse biological problems. Due to the EMBL turnover system, the Unit composition changes rapidly, and the Coordinator plays a critical role in the choice of new Group Leaders and thus in the research direction of the entire Unit. In addition to exciting colleagues, the Heidelberg laboratory, where the position is located, provides excellent shared facilities for high-throughput analysis including micro-arrays, protein production, mass spectrometry, DNA sequencing, advanced light and electron microscopies, small molecule chemical screening as well as state of the art animal facilities.

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Further information on the position can be obtained from the EMBL Director General, Iain Mattaj (dg-office@embl.de).

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Fax: +49 6221 387555

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TOP EMPLOYER SURVEY

1. Innovative Leader in the Industry

Rank	Employer
1	Genentech, Inc.
2	Roche Pharmaceuticals
3	Boehringer Ingelheim

2. Treats Employees with Respect

Rank	Employer
1	Boehringer Ingelheim
2	Genentech, Inc.
3	AstraZeneca PLC

3. Work and Personal Values Are Aligned

Rank	Employer
1	Boehringer Ingelheim
2	Genentech, Inc.
3	Eli Lilly and Company

4. Loyal Employees

Rank	Employer
1	Boehringer Ingelheim
2	Genentech, Inc.
3*	AstraZeneca PLC / Eli Lilly and Company

5. Socially Responsible

Rank	Employer
1	Boehringer Ingelheim
2	Eli Lilly and Company
3	Johnson & Johnson

6. Clear Vision toward the Future

Rank	Employer
1	Genentech, Inc.
2	Boehringer Ingelheim
3	Roche Pharmaceuticals

The companies that have the best records on each of the six major driving characteristics, in the view of survey respondents.
* Indicates tie in firms' scores.

not directly translated into drug development projects, has greatly contributed to our research advances for more than 15 years."

"Roche has a business strategy that builds on innovation and growth," Keller asserts. "Letting the scientific community and the public know how we work in R&D, how we share knowledge within the company and with our partners in the innovation network, and how we develop people helped a lot to attract new talent. As a result, we have improved our position as an employer of choice in many countries."

Roche recognizes the value of good employees. "We will continue the way we have started, and focus on attracting and recruiting good people who can help the company grow and prosper," Keller says. As an inducement, the Roche Connect program enables everyone in the firm to buy the company's nonvoting equity securities at a substantial discount. "Also, we want to be innovative," Keller continues. "Roche was one of the first companies in our industry to introduce a really simple syndication feed for upcoming positions that automatically notified an interested person about upcoming jobs. This year we also worked on full accessibility for disabled people."

Consistent Commitment

Amgen's Perlmutter points to the consistency that has seen the company place regularly in the high five in the survey. "We're extremely consistent in our commitment to our mission," he says. "Our mission is to serve patients; there's no ambiguity in it. We will use innovative science to improve patients' lives. That's a very attractive thing for scientists."

Another consistent performer takes a similar view. "We are proud to continue to be a science-driven company," says Jenni Hardy, AstraZeneca's vice president of human resources for discovery. "We are committed to excellence in how we do research in science. With our new CEO, David Brennan, the agenda of our reputation is at the forefront. The quality of our pipeline drives reputation and we need outstanding employees to strengthen the pipeline."

The criticality of basic science echoes throughout the top 10. "We've been continually successful over time in developing new drugs," says Richard Gregory, head of research at Genzyme. "We're always trying to bring drugs with a real value for patients. That idea permeates all the way back to early discovery in the laboratory." Ginger Gregory, head of human resources at the Novartis Institutes for BioMedical Research, makes the point just as directly. "The primary reason why we should be viewed highly is that we're doing great science," she says. "I believe that, when scientists look at Novartis as a potential employer, they see a company with a great pipeline and an innovative research organization that is focused on helping patients."

Companies that have advanced in this year's top 20 have their own take on the value of basic science. "Increasingly, we're being seen as having had a jump in R&D productivity, in both the late and early stages of our pipeline," points out Bruce Schneider, executive vice president and chief of operations at Wyeth Research. Koestler echoes that sentiment. "It is clearly understood at the very top level of Schering-Plough that we're a science-driven company – that R&D is a critical component of our future success," he says.

Key Drivers

Of course, devotion to basic science alone does not account for the high reputations of companies that made the survey's top 20. Respondents to the survey also took into consideration corporate performance on the key drivers that they identified.

Again, Genentech provides the exemplar for the industry, showing strong performance on all six major drivers. "Those issues reflect our corporate mission," Scheller says. "Our executive committee spends a lot of time discussing these issues, putting together a long-range plan for the company – currently Horizon 2010 – directed toward different areas." The plan gives the company's research department, for example, the task of moving 20 new molecules into clinical development during the period 2005 to 2010. "We've taken great pains to promote this vision broadly across the company," Scheller says.

Genentech has taken a particular step in terms of social responsibility. The company has put increased emphasis on the activities of its Genentech Foundation. "In the last year, the foundation has become more organized, with greater support from the company," Scheller says. "The foundation supports science education, patient groups, and communities in which we operate."

Boehringer Ingelheim believes that its solid performance on the key drivers stems from the fact that it is a private, family-owned company. "Our vision and strategy focus on the long-term CONTINUED »

TOP EMPLOYER SURVEY

development of the corporation and not on short-term effects," Geppert explains. "Last year we explained to all our employees worldwide our 'lead and learn' philosophy, which involves working together and delivering value through innovation."

Roche's approach emphasizes the driving characteristics for which survey respondents regarded the company as particularly effective. "We have developed a clear business strategy built on our values that focuses our efforts on innovation and growth," Keller explains. "Our governance model is based on the belief that, through the decentralized creation of the best ideas, autonomy of decision making, and using innovative tools and technologies, we can best sustain a consistent delivery of new, clinically differentiated medicines that really make a difference in patients' lives."

Coherent Set of Principles

Amgen attributes its high scores on the characteristics of innovative leadership, loyal employees, and clear vision to its corporate policies. "We have a very coherent set of principles with respect to both Amgen itself and the R&D organization," Perlmutter points out. "We have a mission to serve patients, an aspiration to do that better than anyone in the world, and an ambition to be science-based in all our deliberations. We also have a set of leadership attributes aligned with people who have scientists in mind." The company particularly emphasizes innovation in its products. "We are testing pathways that haven't been tried before, in 90 percent of the molecules that we have brought to the clinic," Perlmutter continues.

AstraZeneca agrees with survey takers who peg social responsibility as a particularly critical factor in its operations. "We're very proud of the fact that we're an ethical organization and that our stakeholders want to develop a relationship with us," Hardy says. Yates points to AstraZeneca's work in the developing world. "TB is the single largest cause of adult death from infectious disease in the world," she notes. "We are the only pharmaceutical company with a research program in India totally dedicated to TB."

Genzyme's strong reputation for innovative leadership and clear vision plays out in its emphasis on patients. "We make drugs from the start that have a dramatic effect on patients' lives," Richard Gregory says. "We're also a pretty innovative company. We have a huge array of technology platforms. We're working on proteins and antibodies, gene therapies, and small molecules."

The company also puts serious effort into maintaining its R&D talent. "We're known as being a very family-friendly company, in terms of job sharing and leaves – just being a company that takes the employees' lives outside the company into consideration," Gregory continues.

Clear Corporate Vision

Ginger Gregory at Novartis makes similar points about the value of having a clear corporate vision and treating employees with respect. "Once we've spent time and energy recruiting talent, we want to help our associates be successful both scientifically and professionally," she says. "We want them to understand various career paths. We want to provide them with the tools they need, such as mentoring and other programs to help them understand various career paths and opportunities in the company. One example is a sabbatical program that allows people to leave their role and go into another disease or study another technology for six months or longer."

For Wyeth, social responsibility appears both in this survey as a major driver and in corporate policy. "Social responsibility has become much more talked about in the last couple of years than in the past," Schneider says. "For example, we are working with the World Health Organization to develop Moxidectin, a new product to treat river blindness in Africa. We have programs to make our key product lines available to people who can't afford them. We also try to be good corporate citizens in the communities in which we operate."

Respondents pegged innovation and loyal employees as key drivers that helped Schering-Plough to crack the top 20. Koestler agrees. "Science is the DNA of our culture," he says. "We have a culture of innovation in which traditional ways are challenged. We aim to meet unmet medical needs." Employees' loyalty stems in part from the company's diversity. "We have 46 percent of our work force as women and minorities, including 25 percent in our United States work force," Koestler explains. "*Working Mother* magazine selected us as one of the best companies for working women, and *Fortune* magazine selected us as one of the 50 best companies for diversity."

Negatives, Positives, and Recommendations

What events do survey takers think have had the greatest impact on the reputation of the pharma/biotech industry? As they did last year, respondents pointed to several negatives. Notably they highlighted recalls of drugs that had previously received approval from the U. S. Food and Drug Administration and other regulatory bodies. Respondents particularly mentioned the continuing fallout from the saga over the recall of Vioxx. High profile failures of clinical trials also cast a negative light on the industry, in the view of survey takers. In this instance, they mentioned the collapse of TeGenero Ag's fateful small-scale trial of its drug TGN1412.

Respondents don't paint an entirely bleak picture, however. They see plenty of positive impact in new products and other developments in the industry. Items worthy of mention in this context include new drugs for cancer, new therapies for rare diseases, progress in HIV medications, and stem cell research.

Survey takers also recommended actions that the industry can take to improve its reputation. Openness and honesty head the list. Among respondents' comments: "Inform the public;" "Be honest;" "Be more forthcoming;" "Be open and clear." Other recommended actions include more research, especially collaborative work, and more funding for that research; practicing integrity and high ethics; and controlling costs in such a way as to reduce the prices of drugs.

Despite their cautionary comments, survey takers took a generally rosy view of their own experience in the pharma/biotech industry. As the main advantages, many mentioned the opportunity to impact the world by changing peoples' lives and the ability to participate in cutting-edge science on the forefront of drug development. Other advantages of working in the field include salary and benefits packages, and the job security that the industry provides. Just as important, perhaps, respondents mentioned no specific disadvantage of working in the industry.

A former science editor of Newsweek, *Peter Gwynne writes about science and technology from his base on Cape Cod, Massachusetts, U.S.A.*

You can find an expanded version of this supplement at http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/2006_10_20/science_2006_top_employer_survey_it_all_starts_with_science

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Making a difference.

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Roche

Dunedin, New Zealand

Lecturer/Senior Lecturer/ Associate Professor

(Confirmation Path)

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo

Department of Pharmacology and Toxicology
Otago School of Medical Sciences

The Department of Pharmacology and Toxicology is seeking to make a confirmation path appointment to faculty. We are seeking applicants with an established international research output and a track record in attracting research funds in topical themes in pharmacology or toxicology. The capacity to teach pharmacology and or toxicology to health science and pharmacology students in our undergraduate and postgraduate programmes is an essential element of the post.

Specific enquiries may be directed to Professor George Lees, Head of Department, Tel 64 3 479 7256, Fax 64 3 479 9777, Email george.lees@stonebow.otago.ac.nz

Reference Number: A06/183.
Closing Date: Wednesday 15 November 2006.

APPLICATION INFORMATION

With each application you must include an application form, an EEO Information Statement, a covering letter, contact details for three referees and one copy of your full curriculum vitae. **For an application form, EEO Information Statement and a full job description go to: www.otago.ac.nz/jobs** Alternatively, **contact the Human Resources Division, Tel 64 3 479 8269, Fax 64 3 479 8279, Email** job.applications@otago.ac.nz

EEO Employers Group Equal opportunity in employment is University policy.

www.otago.ac.nz/jobs

TENURE-TRACK FACULTY ASSISTANT/ASSOCIATE/FULL PROFESSOR POSITIONS
Department of Molecular Genetics

The Molecular Genetics Department at The Ohio State University invites applications for full time tenure-track positions. One position will be at the Assistant or Associate Professor rank. Preference for this position will be given to candidates with research interests in **cellular and/or developmental biology** employing model genetic organisms. A second position(s) will be at the Associate or Full Professor rank. Preference for this position will be given to candidates with research interests in **RNA and genomics/proteomics** using model genetic systems. The successful candidates will be expected to have an outstanding novel research program and a commitment to education at the undergraduate and graduate levels.

The Department of Molecular Genetics is a vigorous and highly interactive department that plays a central role in the molecular life sciences on campus. The department consists of faculty members studying important problems in molecular, cellular, and developmental biology using a variety of model organisms including plant and animal viruses, fungi, plants, worms, insects, mice and humans. Departmental faculty members participate in numerous campus-wide collaborations and focus groups such as the Cell Biology Group, the Developmental Genetics Group (**http://groups.yahoo.com/group/dgmeet/**), and the RNA group (**http://www.biosci.ohio-state.edu/~rnaclub/**). Considerable resources are being provided to the new chair of the department, **Dr. Anita Hopper** (**http://www.biosci.ohio-state.edu/news/news-ahopper-chair.php**), to further enhance this excellent department. The Ohio State University is the flagship institution of the state's higher education system. It is located in the state capital, Columbus. Columbus has been ranked as one of the country's best places to live and work. Information about the Department, the University and Columbus can be obtained at: **http://www.osumolgen.org/**.

Applicants should submit a curriculum vitae, a brief description of research interests and future directions, and the names and contact information for at least three professional references. Submit electronic applications to: **siegman.1@osu.edu** or paper applications to: **Molecular Genetics Faculty Search Committees, Department of Molecular Genetics, 984 Bioscience Building, 484 West 12th Avenue, Ohio State University, Columbus, OH 43210**. Review of applications will begin **November 1, 2006** and will continue until the positions are filled.

The Ohio State University is an Equal Opportunity, Affirmative Action Employer. Flexible work options available.

Assistant/Associate Professor Pulmonary Biology

The UC Davis Department of Anatomy, Physiology and Cell Biology in the School of Veterinary Medicine invites applications for a tenure-track faculty position at the level of Assistant/Associate Professor. PhD and advanced training in vertebrate pulmonary biology required. DVM preferred. The successful candidate will be expected to participate in DVM professional and graduate academic program teaching and to develop a creative, independent, productive and externally funded research program in the area of pathophysiology of pulmonary diseases.

Please submit applications including (1) letter of intent outlining special interest in the position, overall related qualifications, experience, and teaching/research goals; (2) curriculum vitae; (3) three representative reprints; and (4) the names and addresses (including e-mail address) of three professional references by **January 5, 2007** to: **Dr. Robert J. Hansen, Department Chair, Department of Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California, One Shields Avenue, 1325 Haring Hall, Davis, CA, 95616, rjhansen@ucdavis.edu**. Electronic applications encouraged.

UC Davis is an Equal Opportunity/ Affirmative Action Employer.

Director, Center for Nanotechnology in Drug Delivery
School of Pharmacy
University of North Carolina at Chapel Hill

The School of Pharmacy, University of North Carolina at Chapel Hill, is seeking to fill the position of Director of a newly created Center for Nanotechnology in Drug Delivery. The successful candidate should have an established funded research program and academic qualifications for appointment at the rank of Associate or Full Professor with tenure in the Division of Molecular Pharmaceutics. UNC, together with regional universities, has many well-established investigators in nanotechnology and related fields. The School of Pharmacy is currently undergoing an aggressive growth and expansion. The Director is expected to establish a highly active and well-funded research center in this intellectually rich, progressive and collaborative environment. More information about the School and the Division can be found at **www.pharmacy.unc.edu**.

Applicant review will begin immediately and the deadline for application submission is **November 30, 2006**. Interested individuals should submit by email a curriculum vitae, Research Summary and 4 names of reference to either **Drs. Moo Cho** (chair of the search committee) or **Leaf Huang** (chair of the Division) at **angela_lyght@email.unc.edu**.

Moo Cho, PhD
Chair, Search Committee
Division of Molecular Pharmaceutics
UNC School of Pharmacy
CB# 7360, Beard Hall
Chapel Hill, NC 27599-7360

The University of North Carolina at Chapel Hill is an Equal Opportunity Employer. Women and members of minority groups are encouraged to apply.

Mathematical, Physical and Life Sciences Division

UNIVERSITY OF OXFORD

Department of Physics in association with Green College

University Lecturer in Biological Physics

Salary will be on a scale up to: £50,589 p.a.

The Department of Physics proposes to appoint a University Lecturer in Biological Physics with effect from 1st October 2007, or as soon as possible thereafter. You will be offered a non-tutorial fellowship by Green College.

Preference will be given to applicants with a strong background in single molecule biophysics, biological self assembly, bio-nano devices including micro- and nanofluidic systems, or topics within nanomedicine such as biophysical approaches to diagnostics and drug delivery.You will be expected to carry out research in biological physics and to participate in the teaching and administrative work of the Physics Department and of Green College.

Further particulars, containing details of the application procedure and of the duties, are available on the department website http://www.physics.ox.ac.uk/cm/vacancies.htm or from Prof. Andrew Boothroyd, Clarendon Laboratory, Parks Road, Oxford OX1 3PU, tel. +44 (0)1865 272225, a.boothroyd@physics.ox.ac.uk

Applicants should submit nine copies (one in the case of applicants based overseas) of a letter of application supported by a CV and statement of research interests, together with the names of three referees (not more than two from the same institution). The application should be sent to Prof. Boothroyd at the above address to arrive no later than 15th December 2006. Applicants should arrange for their references to be sent directly to the above address by the same date. Please quote reference 027/DK06 on all correspondence.

The University is an Equal Opportunities Employer.

www.ox.ac.uk/jobs

CANCER DIAGNOSIS PROGRAM
PROGRAM DIRECTOR
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

The Cancer Diagnosis Program (CDP) is an extramural program within the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) responsible for facilitating the translation of new knowledge in cancer biology and technologies into clinically useful diagnostic and predictive tests. CDP initiated the Program for the Assessment of Clinical Cancer Tests (PACCT) in 2000 to ensure that the next generation of biomarkers and laboratory tests improve the management of cancer patients. CDP works closely with other NCI units and with other government agencies that focus on related aspects of the diagnosis challenge. These include the Cancer Therapy Evaluation Program (CTEP), responsible for the NCI's clinical trials program; the Cancer Imaging Program, responsible for improvements in the non-invasive imaging of tumor physiology and biochemistry; staff from various programs involved in the development of state-of-the art informatics systems, and statistical and mathematical techniques adequate for the analysis of massive datasets; other components of the NCI; the National Institute of Standards and Technology; and such regulatory agencies as the FDA. Since the movement of new diagnostic and predictive tests into clinical practice also depends on interactions with the international oncology community, CDP also fosters collaborations with foreign oncology groups.

CDP is seeking an M.D., Ph.D. or D.O. to serve as a Program Director in the Diagnostics Evaluation Branch (DEB) to participate in a dynamic extramural research program of international scope. Experience with clinical trials and an interest in diagnosis and/or predicting the response to treatment, particularly as it relates to evaluation of biomarkers and in vitro diagnostic tools is necessary. The Program seeks an individual with experience in the translation of new knowledge and technology to clinical practice. A knowledge of systems biology and bioinformatics especially as it relates to identification of biomarkers or groups of biomarkers is helpful. Also helpful is experience that involves understanding the clinical decisions that can be informed by the use of markers and molecular technologies. The candidate will work with the Chief of the Diagnostics Evaluation Branch of the CDP and staff in the development of new initiatives for both the academic and business research communities. Significant effort will be devoted to projects initiated as part of PACCT.

Base salary for this position ranges from $91,407 to $118,828 per annum. MD and DO candidates are eligible for an additional allowance beginning at $13,000 per annum, depending on qualifications. Benefits include health and life insurance options, retirement, paid holidays and vacation leave.

To apply for this position, please visit: **http://jobsearch.usajobs.opm.gov/a9nih.asp** and keyword search for Vacancy Announcements **(VA), NCI-06-142673 (Ph.D.) or NCI-06-142674-DH (MD or DO)** for the mandatory application requirements. You must apply by the closing date of **October 30, 2006**. For questions about applying to the VA, please contact **Mary Lou Weathers, on (301) 402-5059 or weatherm@mail.nih.gov**.

For more information about the position, please contact **J. Milburn Jessup, MD at jessupj@mail.nih.gov or (301) 435-9010**.

Department of Health & Human Services (DHHS)
National Institutes of Health (NIH)
National Institute of Dental and Craniofacial Research (NIDCR)

The National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH), Department of Health & Human Services (DHHS) is seeking applicants for a Biologist/Microbiologist/Health Scientist Administrator position in the Center for Integrative Biology and Infectious Diseases (CIBID). The position advertised is for the Director of the Microbiology Program. This program supports extramural basic and translational research on the role of oral microbes in health and disease. To this end, four broad scientific areas provide the basis for rapid development of knowledge of the etiology, pathogenesis, diagnosis, treatment and prevention of oral infectious diseases. These interrelated areas are: (i) Biofilms and Microbial Ecology; (ii) Microbial genomics; (iii) Microbial Virulence and Disease Pathogenesis; and (iv) Prevention and Treatment.

The incumbent will direct, administer and evaluate a portfolio of extramural grants, contracts and cooperative agreements and will stimulate interest in and provide advice to the extramural community regarding the respective research portfolio. In addition, the incumbent will participate in funding decisions, policy development, as well as implementation and coordination with other programs both within and outside of the NIDCR.

The salary range for this position is $77,353 to $118,828 per annum, commensurate with qualifications and professional experience. A full benefits package is available, which includes retirement, Thrift Savings Plan participation, health, life and long-term care insurance.

For qualifications required, evaluation criteria, and application instructions, view the vacancy announcements at: **http://jobsearch.usajobs.opm.gov/a9nih.asp**. Refer to announcement **# NIDCR-06-141634DE** or **NIDCR-06-147841MP**. Applications will be accepted until **October 27, 2006**. Please contact **Michelle Lipinski at 301-594-2286** or **lipinskim@od.nih.gov** if you have questions.

Positions @ NIH
THE NATIONAL INSTITUTES OF HEALTH

HELP US HELP MILLIONS

Department of Health and Human Services (DHHS)
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)

The National Institute of Allergy and Infectious Diseases (NIAID), the second largest institute of the world-renowned National Institutes of Health (NIH), supports and conducts basic and applied research to better understand, treat, and prevent infectious, immunologic, and allergic diseases.

The Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases.

DALE AND BETTY BUMPERS
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
Vaccines for Life™

Viral Immunology

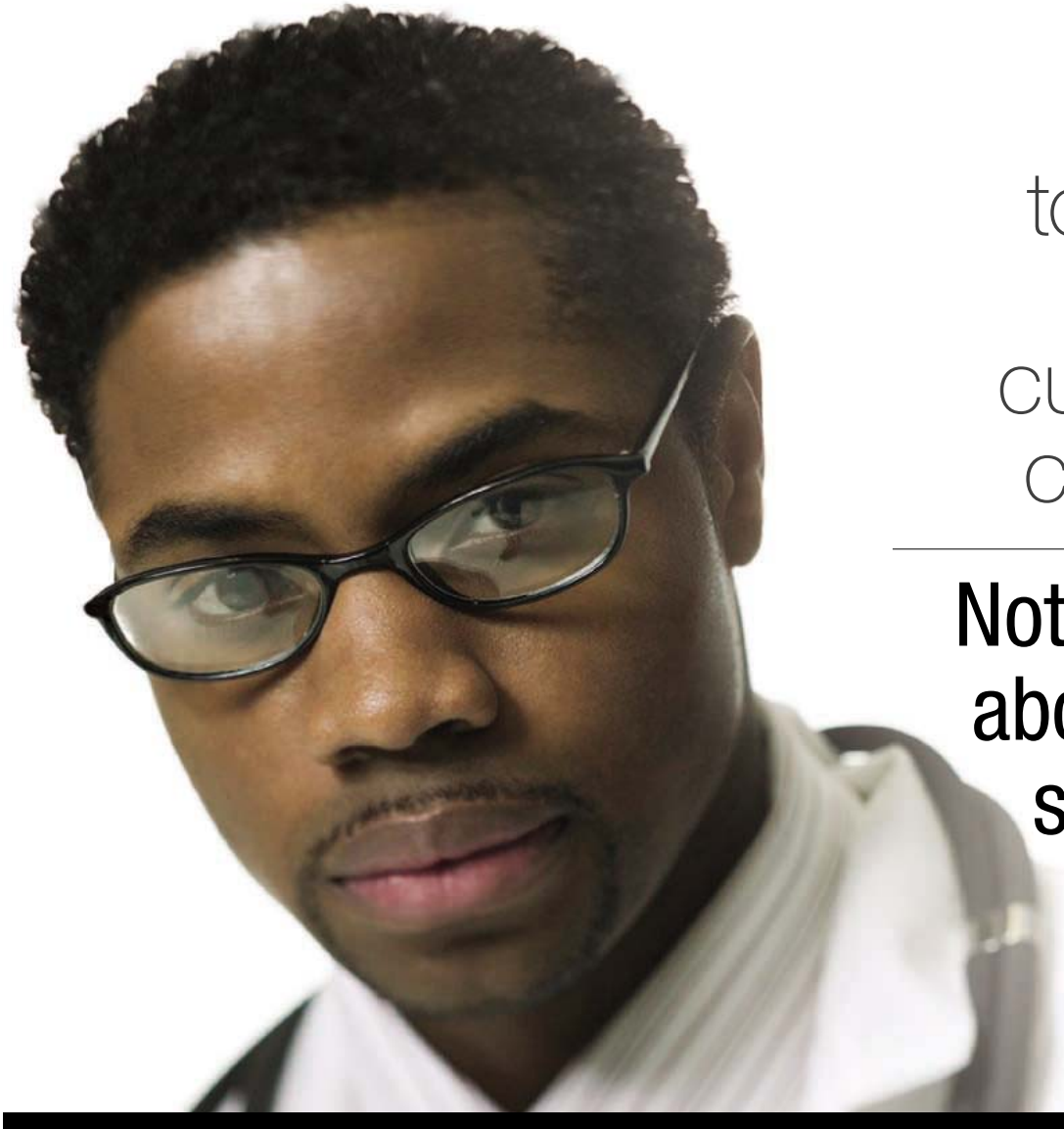
The Vaccine Research Center/Biodefense Research Section is **seeking motivated individuals** to study cellular and molecular mechanisms of immune protection from filovirus infection. The primary focus is on using non-human primate models to understand T-cell and humoral anti-viral immunity to Ebola and Marburg virus. Current projects use 12-color flow cytometry and molecular techniques to characterize qualitative and quantitative properties of protective immunity in subjects immunized with gene-based filovirus vaccines (Nature 2000, Nature 2003).

Applicants must have a Ph.D./M.D/D.V.M and a strong background in immunology / virology / microbiology. Experience in cellular or molecular immunology is desirable. Interested applicants should send their cover letter, CV and three letters of reference to Dr. Nancy Sullivan, Chief, Biodefense Research Section, NIH Vaccine Research Center, 40 Convent Drive, Bethesda, MD 20892 or by e-mail (nsullivan@nih.gov) for consideration.

Department of Health and Human Services
National Institutes of Health
Director, National Center for Research Resources and
Associate Director for Clinical Research (Extramural)

The Office of the Director, National Institutes of Health (NIH) in Bethesda, Maryland, is seeking applications from exceptional candidates for the position of Director, National Center for Research Resources (NCRR). The Director, NCRR, will also serve as the NIH Associate Director for Clinical Research (Extramural). NCRR, with a staff of approximately 100 employees and a $1 billion budget, is the focal point at NIH for biomedical, clinical and translational research resources. The incumbent serves as a principal advisor to the Director, NIH; participates in discussions relative to the development of major policy decisions affecting biomedical, clinical and translational research resources; provides advice and consultation to NIH components, advisory councils and grantee organizations and institutions; and assures that effective administrative procedures are established so that program operations and obligations of government funds and other resources are rendered consistent with statutory and regulatory requirements and within limitations imposed by the Department of Health and Human Services (DHHS) and Executive Branch policies. As Associate Director for Clinical Research (Extramural), the incumbent is expected to provide leadership for clinical research activities across the NIH. This leadership will involve the coordination of clinical research activities to enhance the integration of basic and clinical research. The Associate Director for Clinical Research will work closely with the other Institute and Center Directors to enhance the efficiency and effectiveness of clinical research supported by the NIH. Applicants must possess a Ph.D., M.D., or a comparable doctorate degree in the health sciences field plus senior level scientific experience and knowledge of biomedical, clinical and/or translational research programs in one or more health science areas. Salary is commensurate with experience and a full package of benefits (including retirement, health, life, long term care insurance, Thrift Savings Plan participation, etc.) is available. A detailed vacancy announcement, along with mandatory qualifications and application procedures, can be obtained via the NIH Home Page at: **http://www.jobs.nih.gov** under the Senior Job Openings section. Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and Dr. David Schwartz, Director, National Institute of Environmental Health Sciences, will be serving as co-chairs of the search committee. Questions on application procedures may be addressed to **Ms. Regina Reiter at ReiterR@od.nih.gov or discussed with Ms. Reiter by calling 301-402-1130**. Applications **must** be received by **November 27, 2006**.

WWW.NIH.GOV



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Not worry about my student loans

If you're interested in a biomedical research career, you should know that the National Institutes of Health Loan Repayment Programs may repay up to $35,000 per year of your qualified educational loan debt.

Deadline for Applications is December 1

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The NIH Loan Repayment Programs | *Healthier Futures Through Research*

Positions @ NIH

The National Institutes of Health

The National Institute of Allergy and Infectious Diseases, a major research component of the NIH and the Department of Health and Human Services, is recruiting a Staff Scientist. The position will be available in the Respiratory Viruses Section of the Laboratory of Infectious Diseases, and scientists with a M.D., D.V.M, or Ph.D. are eligible. The research activity involves (1) examination of the pathogenesis of pandemic and potential pandemic strains of influenza and their evaluation in vitro and in experimental animals; (2) influenza viral genomics, and examination of viral evolution in fitness and host adaptation; and (3) the development of influenza clinical trials in humans. This full-time research position offers a unique opportunity to work on investigations that range from basic molecular biology to clinical research. Staff Scientist applicants should have at least six years of laboratory work experience in molecular and classical virology research; the salary range is $73,178 - $165,195. Preference will be given to candidates who have experience working with avian influenza viruses and those with BSL3 experience. Applicants should submit their curriculum vitae, a letter of research interests, and names and addresses of three references to:**Jeffery K. Taubenberger, MD, PhD, Attn: D. Kyle, NIAID, NIH, Bldg 50 Room 6234, MSC 8007, 50 South Drive, Bethesda, MD 20892-8007, FAX: (301) 496-8312, email: dkyle@niaid.nih.gov**

Review of applicants will begin on **October 30, 2006** and continue until a successful candidate is identified.

The National Institute of Allergy and Infectious Diseases, a major research component of the NIH and the Department of Health and Human Services, is recruiting a Staff Scientist. The position will be available in the Respiratory Viruses Section of the Laboratory of Infectious Diseases, and scientists with a M.D., D.V.M, or Ph.D. are eligible. The research activity involves (1) the development of live attenuated vaccines against potential pandemic strains of influenza and their evaluation in experimental animals as well as in clinical trials in humans; (2) examination of the pathogenesis of avian influenza viruses and SARS-coronavirus; (3) the evaluation of the immunologic determinants of resistance to infection and disease caused by influenza viruses and SARS-coronavirus. This full-time research position offers a unique opportunity to work on investigations that range from basic molecular biology to applied vaccinology. Staff Scientist applicants should have at least six years of laboratory work experience in molecular virology and vaccine research; the salary range is $73,178 - $165,195. Preference will be given to candidates who have experience working with avian influenza viruses. Applicants should submit their curriculum vitae, a letter of research interests, and names and addresses of three references to: **Kanta Subbarao, MD, MPH, Attn: A. LeCointe, NIAID, NIH, Bldg 50 Room 6234, MSC 8007, 50 South Drive, Bethesda, MD 20892-8007, FAX: (301) 496-8312, email: lecointe@niaid.nih.gov**

Review of applicants will begin on November 1, **200**6 and continue until a successful candidate is identified.

Head, Gene Delivery Core Facility
Research Triangle Park, North Carolina

The NIEHS/NIH, in RTP, North Carolina, is recruiting a Staff Scientist in the Laboratory of Neurobiology to manage a new Gene Delivery core facility in the Division of Intramural Research. The successful applicant will be responsible for designing, producing, and validating viral vectors to allow temporally and spatially controlled gene expression and inactivation in mice, their tissues and cells. Additional duties will include serving as a molecular biology expert during the planning and execution of experiments with Institute scientists; and supervising and training Institute laboratory personnel in the safe and effective production and laboratory application of these vectors.

Minimum qualifications include a PhD and at least ten years of experience using viral vectors and recombinant DNA to solve problems of biomedical interest. In particular, the applicant must demonstrate experience independently directing their own work and the work of others. Applications from under represented groups are particularly encouraged. Interested parties should submit a curriculum vitae, bibliography, brief statement of relevant background and arrange for the submission of three letters of recommendation to be sent by **November 20, 2006** to: **Ms. Cindy Garrard (DIR-06-07), National Institutes of Health, National Institute of Environmental Health Sciences, P.O. Box 12233, Mail drop A2-06, 111 Alexander Drive, Room A206, Research Triangle Park, NC 27709, E-mail: dir-appls@niehs.nih.gov**

NIDDK

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK POSTDOCTORAL POSITIONS within the Molecular and Clinical Hematology Branch are available to study hematopoiesis and hemoglobin switching. Current projects include studies of the molecular basis of lineage-specific differentiation of hematopoietic stem cells and the development of therapies for hemoglobinopathies and other genetic blood disorders. A strong background in molecular biology, cell biology and/or signal transduction is required. Opportunities exists to develop relevant clinical or translational projects. Salary and benefits will be commensurate with experience of the applicant. Interested candidates with an M.D. and/or Ph.D., and less than five years of postdoctoral experience should send a CV, bibliography, and names of three references to: **Griffin P. Rodgers, M.D. at (gr5n@nih.gov) or: Molecular and Clinical Hematology Branch, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 10 Center Drive, Building 10, Room 9N-119, Bethesda MD 20814**.

WWW.NIH.GOV

Department of Health and Human Services
National Institutes of Health
National Institute of Allergy and Infectious Diseases

With nation-wide responsibility for improving the health and well being of all Americans, the Department of Health and Human Services oversees the biomedical research programs of the National Institutes of Health (NIH) and those of NIH's research Institutes.

The National Institute of Allergy and Infectious Diseases (NIAID), a major research component of the NIH and the Department of Health and Human Services, is recruiting for a Tenure/Tenure Track position in the Laboratory of Host Defenses (LHD). The LHD studies immune functions essential for host defense against infection (inherited immune deficiencies) and those required for immune homeostasis (autoimmunity associated with excessive inflammation). The LHD seeks an M.D. or M.D., Ph.D. physician scientist to develop an independent translational research program related to the genetic basis, pathophysiology, diagnosis and treatment of autoimmune diseases associated with excessive inflammation. An emphasis on clinical aspects of innate immunity including phagocytic cells, natural killer cells, dendritic cells and other antigen presenting cells, toll-like receptors or other pattern recognition receptors in its interface with acquired immunity is desirable. The applicant should have a strong track record of basic research of the genetic basis of disease and alterations in signaling pathways responsible for immune dysregulation. The applicant must possess expertise and experience in the design and conduct of diagnostic and therapeutic clinical trials studying and treating autoimmune diseases. Strong clinical credentials in a specialty area relevant to the proposed translational research program (relevant specialties include but are not limited to rheumatology, pulmonary diseases, hematology, immunology or infectious diseases) are required. The program of study proposed by the applicant must include both laboratory components and the conduct of clinical protocols to assess new diagnostic and therapeutic modalities to diagnose and treat autoimmunity associated with excessive inflammation. Applicants particularly suitable for this program are those who have knowledge and experience in the development and clinical application of novel biological agents including chemokines, soluble chemokine receptors, adenosine receptor agonists, monoclonal antibodies, cellular therapies including transplantation or gene therapy to correct the abnormalities in immunity, that achieve immune tolerance or to reduce abnormal inflammation.

The applicant must provide evidence in the submitted materials that the applicant has a current license to practice medicine in one of the states of the United States or must have all the credentials required by the State of Maryland for licensing to allow the practice of medicine. These credentials must include but are not limited to having a Doctor of Medicine or Doctor of Osteopathy degree from an accredited school in the U.S. or Canada, or a Doctor of Medicine or equivalent degree from a foreign medical school that provided education and medical knowledge substantially equivalent to accredited schools in the U.S. as demonstrated by permanent certification by the Educational Commission for Foreign Medical Graduates (ECFMG).

To be considered for this position, you will need to submit a curriculum vitae, bibliography, three (3) letters of reference, a detailed statement of research interests, and a hardcopy of selected publications to **Thomas A. Fleisher, MD, Chairperson, NIAID Search Committee, c/o Ms. Anissa N. Hunter, DIR Committee Coordinator, Reference Ad #009, 10 Center Drive MSC 1356, Building 10, Rm. 4A26, Bethesda, Maryland 20892-1356 or via e-mail at huntera@niaid.nih.gov**. Completed applications **MUST** be received by **Thursday, November 15, 2006**. For additional information on this position, and for instructions on submitting your application, please see our website at: **www.niaid.nih.gov**.

West Virginia University
ROBERT C. BYRD HEALTH SCIENCES CENTER

Faculty Positions
Center for Interdisciplinary Research in Cardiovascular Sciences

As part of a major interdisciplinary initiative in cardiovascular research, the West Virginia University Health Sciences Center invites applications from outstanding scientists for multiple tenure-track positions, available July 1, 2007. This recruitment is open to all ranks, but we are especially interested in individuals with established research programs, to be appointed at the Associate or Full Professor rank. We seek investigators with a cardiovascular and/or cardiorenal emphasis, whose research programs will complement our existing strengths in:

- cardiomyocyte dysfunction
- mechanisms of impaired vascular reactivity
- endothelial barrier integrity
- microvessel network formation/remodeling

Individuals utilizing experimental approaches incorporating novel stem cell/progenitor cell techniques, molecular genetics or computational modeling of physiological systems into their research programs are especially encouraged to apply.

Appointees for Assistant Professor will be expected to develop a competitive, NIH-funded, independent research program; appointees for Associate or Full Professor will be expected to have current NIH funding. Appointees will also be expected to participate in the teaching mission of the institution. The successful candidate will receive a generous startup package, competitive salary, and fully renovated laboratory space commensurate with experience and qualifications. An appointment in the most suitable basic science or clinical department will be provided.

A major goal of this interdisciplinary center (**http://www.hsc.wvu.edu/circs**) is to develop collaborations among basic, translational and clinical research in cardiovascular health and disease. The Health Sciences Center supports excellent core facilities that include proteomics and protein mass spectrometry, confocal microscopy, functional imaging, flow cytometry, histology, and mouse transgenics. West Virginia University is a comprehensive, Carnegie designated Doctoral Research-Extensive, public institution. Morgantown is rated as one of the best small towns in the U.S., with affordable housing, excellent schools, a picturesque countryside, and many outdoor activities.

Minimum Qualifications: Ph.D., MD, or MD/Ph.D., two or more years of postdoctoral training, and evidence of significant peer-reviewed research accomplishments. Interested individuals should submit a complete curriculum vitae, a brief description of research interests, and the names and addresses (including e-mail) of three references to: **Jefferson C. Frisbee, Ph.D., Center for Interdisciplinary Research in Cardiovascular Sciences, PO Box 9105, West Virginia University, Morgantown, WV 26506-9105**. Review of applications will begin immediately and continue until positions are filled.

West Virginia University is an Affirmative Action/ Equal Opportunity Employer.

UNIVERSITY OF DELAWARE

One of the oldest institutions of higher education in this country, the University of Delaware today combines tradition and innovation, offering students a rich heritage along with the latest in instructional and research technology. The University of Delaware is a Land-Grant, Sea-Grant, Urban-Grant and Space-Grant institution with its main campus in Newark, DE, located halfway between Washington, DC and New York City. Please visit our website at **www.udel.edu.**

Assistant or Associate Professor(s)
Clean Energy, Nanotechnology, Bioengineering and MicroRobotic Networks

The Departments of Electrical and Computer Engineering and Mechanical Engineering invite nominations and applications for two tenure-track faculty positions in the general areas of (1) Clean Energy and Energy Storage, (2) Nanotechnology, (3) Bioengineering, and (4) Micro-robotic networks.

Each faculty position will hold joint appointments in the Department of Mechanical Engineering (ME) and the Department of Electrical and Computer Engineering (ECE) and will become part of a broad interdisciplinary research program within the College of Engineering. Nanotechnology initiatives are supported by a fully equipped new state-of-the art 7,000 sq ft clean room for nano-fabrication with over $10M/year in research expenditures. Some nanotechnology work is done in our Center for Composite Materials, which boasts $8 million of research funding per year and 240 affiliated faculty, staff, post-docs, graduate and undergraduate students and interns. Bioengineering activities are closely coupled to the inter-disciplinary effort at the Delaware Biotechnology Institute that encompasses research, education, and economic development in the life sciences with emphasis on human health, complex environmental systems and biomaterials. This $120M initiative involves a 72,000 sq ft state-of-the-art biotechnology facility. In addition, the new faculty can be a part of our Center for Biomedical Engineering Research, which has 33 associated faculty members and many NIH grants, including an NIH Center for Biomedical Research Excellence (COBRE) award. The solar, fuel cell and other clean energy research at UD is world renowned, having over $9M/year in research expenditures, and supported by state-of-the-art fabrication facilities.

Applicants should hold a Ph.D. in mechanical, electrical, or computer engineering, or closely related physical sciences. Successful candidates are expected to have demonstrated excellence in innovative research and show the potential for high quality teaching and mentoring. The appointment is anticipated to be at the tenure-track assistant or associate professor level, however, qualified candidates at all levels will be considered.

Applicants should email a curriculum vitae, a statement of research and teaching interests and achievements, and a list of at least four references to f-search@udel.edu; or mail to ECE/ME Faculty Search Committee, 140 Evans Hall, University of Delaware, Newark, DE 19716. Review of applications will begin on November 15, 2006 and will continue until the position is filled. The curriculum vitae and all application materials shall be shared with departmental faculty.

The UNIVERSITY OF DELAWARE is an Equal Opportunity Employer which encourages applications from Minority Group Members and Women.

The Ohio State University

Insect Population Geneticist/ Agronomic Crops

Department of Entomology
www.oardc.ohio-state.edu/entomology

POSITION TITLE: Assistant Professor, tenure track, 12-month appointment, 70% research/ 30% extension.

LOCATION: Department of Entomology, The Ohio State University, Ohio Agricultural Research and Development Center (OARDC), Wooster (http://www.oardc.ohio-state.edu/centernet/)

POSITION DESCRIPTION: We are seeking a broadly trained Population Geneticist with excellent molecular and quantitative skills, to address population genetics or genomics with concentration in management of insect pests of agronomic crops. Research could focus on gene flow among insect populations, resistance management, metapopulation dynamics of above or below ground insects, invasive species or other questions of importance to state, national and international interests. The person will also conduct a dynamic extension education program focused on crop traits relevant to insect pests and their use in managing Ohio agroecosystems; collaborate with faculty and staff in entomology and in other departments, county extension educators, and Ohio's field crop industries on projects of mutual interest. The successful candidate will be an active member of OSU's interdisciplinary extension/research Agronomic Crops Team (http://agcrops.osu.edu/) and regional research committees. The incumbent will be expected to seek both internal and external research and extension program support from government, industry, and other sources. The incumbent will be expected to have a strong commitment to graduate education. A willingness to respond to the needs of Ohio's agricultural clientele is essential.

MINIMUM QUALIFICATIONS, EXPERIENCE, SKILLS AND ABILITIES: Ph.D. in Entomology, Genetics, or related field; evidence of scholarly achievement; evidence of research and training in the population genetics; excellent quantitative skills; experience in molecular techniques applied to research at the population level; excellent written and oral communication skills; evidence of ability to generate extra-mural grant funding, ability to work in interdisciplinary teams, and a strong interest in outreach/extension activities.

DESIRABLE EXPERIENCE, SKILLS AND ABILITIES: Post-doctoral experience, familiarity with agronomic crop production systems and current technology; experience with interdisciplinary, inter-institutional and/or international collaborations; experience with integration of basic and applied research; and experience with extension and outreach education.

FOR MORE INFORMATION OR QUESTIONS REGARDING THE POSITION:
Please contact either **Dr. Parwinder Grewal, search committee chair (330.263.3963, grewal.4@osu.edu) or Dr. Susan Fisher, department chair (614.292.8209, fisher.14@osu.edu).**

APPLICATIONS: Review of applications will begin January 1, 2007. Applications will be accepted until a suitable candidate is found. Applicants must submit a complete curriculum vitae, copies of academic transcripts, relevant publications, a statement of research interests and approach to extension, and the names, addresses, phone numbers and email addresses of 3 references to: **Dr. Parwinder Grewal, Search Committee Chair, Department of Entomology, The Ohio State University, 1680 Madison Ave., Wooster, OH 44691. Phone: 330.263.3963; Fax: 330.263.3686; email: grewal.4@osu.edu.**

THE OHIO STATE UNIVERSITY

To build a diverse workforce Ohio State encourages applications from individuals with disabilities, minorities, veterans and women. EEO/AA employer.

MRC Medical Research Council

RSA Search & Selection

MRC Director of Clinical Sciences Centre

We invite applications for the Directorship of the Medical Research Council's Clinical Sciences Centre (CSC), to succeed Professor Chris Higgins when he steps down in 2007.

Since its inception in 1994, the CSC has pursued an interdisciplinary research programme aimed at advancing our understanding of human health and disease. First-class programmes in molecular and cell biology, genomics and biological and clinical imaging combine to address fundamental questions and to deliver improvements for disease prevention, diagnosis and treatment. The new Director will be able to capitalise on CSC's internationally competitive programmes, leading and shaping future research strategy.

CSC benefits from close integration with Imperial College London and its high level of investment in translational research. The new Director will provide a vision for basic and clinical research, working with MRC and Imperial College to define a joint programme and will be a Head of Division within the Faculty of Medicine.

The new Director will be expected to provide strong leadership, working with CSC's academic, clinical and industrial partners to create an environment that stimulates productive interactions between basic and clinical scientists and fosters the application of leading edge approaches to clinical research. He/She will also be expected to head an innovative research programme, for which funding will be provided. Wider responsibilities include staff development, resource management and technology transfer.

Applicants should be at Professorial level, with an outstanding scientific record. We are seeking an individual with the energy, interpersonal skills and vision to lead the CSC and inspire a talented group of scientific colleagues. Previous experience of managing a significant research initiative would be desirable and the successful candidate will display a real commitment to fostering links between basic and clinical research programmes.

The appointment salary and other terms and conditions are negotiable. Relocation assistance will be provided where appropriate.

The MRC is an Equal Opportunities Employer.

For further information and to discuss your interest in confidence, please contact Dr Kevin Young on +44 (0)1707 280819 or email your CV to 06722@theRSAgroup.com

Please quote the Ref: 06722S.

RSA, The Melon Ground, Hatfield Park, Hatfield, Herts AL9 5NB Tel +44 (0)1707 259333
rsvp@theRSAgroup.com | www.RSAjobs.com

FACULTY POSITIONS OPEN

INSTITUTE OF MOLECULAR BIOLOGY
ACADEMIA SINICA, TAIWAN, ROC

Two tenure-track faculty positions are open for highly qualified individuals to establish independent research programs in **all areas of molecular and cellular biology** that would complement or strengthen the current topics in the Institute, including biochemistry, structural biology, developmental biology, immunology, and plant biology. However, individuals with innovative approaches that would lead to a new research program are also highly encouraged. Applicants should have a Ph.D. degree or its equivalents, and postdoctoral research experience is preferred. Successful candidates will be appointed at the levels of **Assistant, Associate**, or **Full Research Fellows** (the equivalents of Assistant, Associate and Full Professors in universities), with a generous multi-year start-up fund, followed by annual intramural support.

The Institute of Molecular Biology (**http://www.imb.sinica.edu.tw/en**) is an active and stimulating research environment: well supported by both intramural and extramural funding, providing highly supportive cores such as imaging, genomics, bioinformatics and mouse facility, and maintaining close international connections and strong interactions with local universities. Currently three Ph.D. programs, with one recruiting international students, are formally affiliated with the Institute. English is the official language for regular seminars and most of the lectures in the Institute, and proficiency in the Chinese language is not a prerequisite for application.

Applicants should send their Curriculum Vitae, a description of past research accomplishments and future research interests, and three letters of reference to: **Dr. Meng-Chao Yao, Director, c/o Ms. Vivi Chiang, Institute of Molecular Biology, Taipei, Taiwan 11529, ROC**

The selection process will start on December 31, 2006 until the positions are filled. Further information can be obtained from **Ms. Vivi Chiang at vivi@imb.sinica.edu.tw**

UNIVERSITY OF DELAWARE

One of the oldest institutions of higher education in this country, the University of Delaware today combines tradition and innovation, offering students a rich heritage along with the latest in instructional and research technology. The University of Delaware is a Land Grant, Sea-Grant, Urban-Grant and Space-Grant institution with its main campus in Newark, DE, located halfway between Washington, DC and New York City. Please visit our website at **www.udel.edu.**

Assistant Professor
Molecular Physiology

The Department of Biological Sciences at the University of Delaware invites applications for a tenure-track faculty position at the Assistant Professor level in the area of molecular physiology with particular emphasis on regenerative or developmental biology. A strong focus in molecular and/or genetic techniques is required and research in fish or amphibian models is preferred. The starting date for this position is September 1, 2007 or later.

Requirements for the position include a Ph.D. or equivalent degree and a minimum of two years postdoctoral experience. The person hired will be expected to develop an active research program, pursue extramural funding, and participate in undergraduate and graduate education. The successful candidate will occupy recently renovated lab space with an attached aquarium room and receive a competitive salary and startup package. For information concerning this position, the Biological Sciences department and university and community resources, please visit our website at **www.udel.edu/bio**.

Please submit a description of research interests, curriculum vitae, and the names of three references with contact information through our website at **http://www.udel.edu/bio/news/facultysearch/** or to Dr. Randall Duncan, Chair, Molecular Physiology Search Committee, Department of Biological Sciences, University of Delaware, Newark, DE 19716-1590. Application deadline is November 15, 2006.

The UNIVERSITY OF DELAWARE is an Equal Opportunity Employer which encourages applications from Minority Group Members and Women.

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

The Comprehensive Cancer Center of Wake Forest University
Medical Center Boulevard
Winston-Salem, NC 27157

We offer attractive start-up funds, lab space and a collaborative environment. Send C.V. and statement of research interests to the appropriate contact.

- **Biomedical Engineering**
  Faculty recruited jointly with Cancer Biology
  Contact: **Pete Santago, Ph.D. psantago@wfubmc.edu**
- **Cancer Biology/Genomics**
  Molecular epidemiologist
  Contact: **Frank Torti, M.D. swilder@wfubmc.edu**
- **Cancer Epidemiologist**
  Associate or Full Professor
  Contact: **Lynne Wagenknecht, Dr. PH lwgnkcht@wfubmc.edu**
- **Cancer Survivorship**
  Contact: **Nancy Avis, Ph.D. navis@wfubmc.edu**
- **Center for Human Genomics**
  Statistical genetics of Cancer
  Contact: **Jianfeng Xu, M.D., Dr. PH jxu@wfubmc.edu**
- **Hematology and Oncology**
  Senior investigator to head experimental therapeutics
  Translational medical neuro-oncologist
  Translational medical oncologist; GI/GU focus
  Translational medical oncologist; BMT focus
  Contact: **Bayard Powell, M.D. bpowell@wfubmc.edu**
- **Radiation Biology**
  Assistant/Associate Professor
  Contact: **Mike Robbins, Ph.D. mrobbins@wfubmc.edu**
- **Urology**
  Translational surgical oncologist
  Contact: **Anthony Atala, M.D. aatala@wfubmc.edu**

AA/EOE

MASSACHUSETTS STATE POLICE

Division of Administrative Services
470 Worcester Road,
Framingham, MA 01702

CHEMISTS

Several positions are anticipated for the position of Chemist. Responsibilities include conducting chemical, physical and biological laboratory testing methods, and conducting examinations at crime scenes.

Chemists will work with investigators, attorneys, and other clients of the Crime Laboratory to provide forensic assistance.

Required experience: at least two years of full-time, or equivalent part-time, professional or technical experience in the field of Chemistry. A Bachelors degree or higher in Chemistry or Biochemistry may be substituted for the required experience.

Salary: $1,506 - $1,992 Bi-weekly.

Send resume and cover letter to indicating job code CSC06:

Department of State Police
Office of Diversity & Equal Opportunity,
470 Worcester Rd. Framingham, MA 01702
The Department of State Police is an Equal Opportunity Employer
www.mass.gov/msp

THE UNIVERSITY OF SOUTHERN MISSISSIPPI
DEPARTMENT OF BIOLOGICAL SCIENCES

TENURE-TRACK FACULTY POSITION
DEVELOPMENTAL BIOLOGIST

The University of Southern Mississippi Department of Biological Sciences invites application for a tenure-track assistant professor position in developmental biology. The successful candidates will join our rapidly growing department with strong research programs in cellular and molecular biology, genomics and bioinformatics, organismal biology and ecology. A competitive salary commensurate with qualifications and experience, competitive start up package, new modern lab space, and state-of-the-art facilities will be provided. The successful candidate will have the opportunity to take advantage of resources provided by the Mississippi Functional Genomics Network, a competitively funded NIH consortium that spans the disciplines of genomics, proteomics, cellomics and bioinformatics (**http://mfgn.usm.edu/mfgn/**).

The University of Southern Mississippi, a Carnegie High Research Activity Institution with over 14,000 students, is located in Hattiesburg, Mississippi, near the Gulf Coast and abundant opportunities for outdoor recreation. Hattiesburg is the medical, commercial and cultural center of south Mississippi and is ranked in the top five small metropolitan areas in the United States. The department of biological sciences is comprised of over thirty faculty and offers baccalaureate degrees in biological sciences and marine biology. Over 70 graduate students currently pursue Masters and doctoral degrees. Further information about the department of biological sciences may be found at **http://www.usm.edu/biology/**.

The successful candidate will be expected to establish an active, extramurally funded research program, mentor graduate students and participate in undergraduate and graduate teaching in his or her area of expertise. A doctoral degree in appropriate discipline and postdoctoral research experience are required.

Applicants should submit a letter of application, curriculum vitae, statement of research plans, copies of pertinent reprints and three letters of reference to: **Dr. Glen Shearer, Developmental Biology Search Committee, Dept. of Biological Sciences, The University of Southern Mississippi, 118 College Drive, Hattiesburg, MS 39406-5018**. Review of applications will begin **December 1, 2006** and continue until the position is filled.

The University of Southern Mississippi is an Affirmative Action/Equal Opportunity Employer.

NATIONAL SCIENCE FOUNDATION
DIVISION OF ENVIRONMENTAL BIOLOGY
Program Director in Ecosystem Ecology
Program Director in Systematic Biology

The National Science Foundation's Division of Environmental Biology (DEB) is seeking qualified candidates for permanent positions of Program Director in the areas of ecosystem science (1 position), and systematic biology and biodiversity inventories (1 position). Program Directors are responsible for program planning and administration, and for furthering the goals of the NSF and DEB. More information about DEB can be found on the website: **http://www.nsf.gov/div/index.jsp?div=DEB**.

Applicants must possess a Ph.D. in biology or in an equivalent discipline, plus six or more years of successful research, research administration, or managerial experience beyond the Ph.D. Familiarity with NSF policies and practices, administrative experience, and recognized stature among peers are desirable. Annual salary range is $91,407 to 142,449 depending on qualification and experience.

The announcements E20070003-Permanent (Ecosystem Ecology) and E20070002-Permanent (Systematic Biology), which include position requirements and application procedures are located on NSF's Division of Human Resource Management website at **http://www.nsf.gov/about/career_opps/** or can be obtained by contacting **Ms. June Jones**, telephone: **703-292-8251**. For scientific or programmatic information, contact **Dr. Penelope Firth**, Acting Division Director, telephone: **703 292-8480**; e-mail: **pfirth@nsf.gov**.

NSF is an Equal Opportunity Employer.

THE STATE UNIVERSITY OF NEW JERSEY
RUTGERS

Tenure Track Faculty Positions
Computational Biology, Molecular Biophysics, and Systems Biology

The BioMaPS Institute for Quantitative Biology at Rutgers University invites applications for tenure track faculty positions at the junior or senior level in computational biology, molecular biophysics, and systems biology. The positions will be joint with an affiliated department in the School of Arts and Sciences or in Engineering. Areas of interest include but are not limited to: the structure and function of molecular and cellular machines, biological networks, structural genomics and proteomics. Applicants should submit a cover letter, curriculum vitae, research summary and statement of future research goals, and a statement of teaching experience and interests and arrange for four letters of recommendation to be sent on their behalf. Materials should be submitted electronically as PDF files to: **Dr. Paul Ehrlich, Administrative Director, BioMaPS Institute** (email: **pehrlich@biomaps.rutgers.edu**). Currently BioMaPS Institute faculty hold joint appointments with the Departments of Chemistry, Mathematics, and Physics in the School of Arts and Sciences and the Department of Biomedical Engineering in the School of Engineering at Rutgers University, New Brunswick Campus. For more information about the BioMaPS Institute, the applicant is directed to: **http://www.biomaps.rutgers.edu**. The review of applications will begin on **December 1, 2006**. *Rutgers University is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are especially encouraged to apply.*

DVC LLC
A CSC COMPANY

DynPort Vaccine Company LLC (DVC), a CSC company, is developing vaccines and related products using the biotechnology integrator approach. We are currently experiencing significant growth and are seeking talented professionals to help us expand into new markets.

Sr. Director, Clinical Research
(DLAUTH95922IL33)
Serve as the thought-leader in implementing clinical research and development programs, ensuring compliance to relevant FDA regulations, setting department SOPs, developing strategy/plans/trial designs for DVC programs, and guiding your team in clinical trial execution. MD with board eligibility or certification in infectious diseases or immunology and 10 years post degree experience required.

Associate Medical Director
(JHOTH71816IL33)
Develop and implement clinical research programs. Must have MD/DO degree and training/certification in infectious disease or immunology.

Director, Clinical Operations
(RVSF103936IL33)
Responsible for guidance, oversight, and coordination of clinical operations at DVC. MS degree and 5-10 years of direct clinical trials management experience within the industry required.

Quality Manager
(RVSF113011IL33)
Internal quality manager conducts audits to enhance and improve systems and ensure CGMP compliance. BS/BA degree and 8-10 years related experience.

Sr. Scientist
(IHSTH10269IL33)
Contribute to the development of vaccines as well as the design, integration and execution of non-clinical and clinical testing strategies. Doctorate level training in Microbiology or related discipline.

Proposal Manager
(RVAUW172611IL33)
Develop proposal solutions to support government contracts and commercial bids. MS degree and 3 years experience in each of biotechnology research and writing/editing complex proposals required.

To apply for these opportunities, please visit our career site at **http://www.dynport.com**
EOE, M/F/D/V.

CSC
EXPERIENCE. RESULTS.
CONSULTING SYSTEMS INTEGRATION OUTSOURCING

Faculty Position in Proteomics

The Sealy Center for Molecular Medicine (SCMM) at the University of Texas Medical Branch at Galveston (UTMB) is seeking outstanding candidates for a tenure track, faculty position in proteomics at the level of assistant or associate professor. The ideal candidates will be individuals with extensive experience in biomarker identification using the tools of mass spectrometry, protein/tissue arrays, or other high throughput approaches. The successful applicant will be jointly appointed in the NHLBI Proteomics Center focusing on airway inflammation and the Institute for Clinical and Translational Research. Additional opportunities exist for interactions within centers of scientific excellence in aging, cancer, neurodegenerative diseases, infectious diseases, environmental health, and/or addiction research.

A wide variety of core services is available, including: organic synthesis, computational biology, mass spectrometry, protein expression and purification, molecular biology, X-ray crystallography, and biophysical solution chemistry.

An attractive recruitment package of salary, start-up and newly renovated space will be offered. Interested applicants should submit a curriculum vitae, a summary of research accomplishments and future goals (3-5 pages), and contact information of five references to:

Allan R. Brasier, M.D.
Sealy Center for Molecular Medicine
The University of Texas Medical Branch
8.128 Medical Research Building
Galveston, TX 77555-1055

UTMB is an Equal Opportunity/Affirmative Action Institution which proudly values diversity. Members of all backgrounds are encouraged to apply.

UTMB
The University of Texas Medical Branch

BROWN

Faculty Position in Proteomics and Protein Biophysics Associate or Full Professor Division of Biology and Medicine

The Division of Biology and Medicine at Brown University announces the opening of a senior faculty position, with the start date of July 1, 2007. Qualifications include a Ph.D. or M.D. degree and a track record of excellence in research. Researchers in the fields of mass spectrometry, structural biology (X-ray, NMR, cryo-EM), protein biophysics, and systems biology with an emphasis on viral systems are especially encouraged to apply.

Applicants will be expected to have independent, externally-funded research programs that emphasize proteomic approaches to contemporary biological problems. Applications from physician-scientists are welcome. The applicants will be expected to engage in graduate, undergraduate and/or medical school teaching, and will have the opportunity to participate in several NIH-funded training programs. Research space will be provided in a new, state-of-the-art facility. The faculty position is part of an ongoing interdepartmental strategic initiative whose objective is to spearhead contemporary biomedical research and to coordinate multidisciplinary approaches in basic science with clinical programs at affiliated hospitals.

Applications will be treated with confidentiality and need not include letters of recommendation; a list of references may be requested by the search committee at a later date. Review of applications, which should include a curriculum vitae and a description of research interests, will commence on **December 1, 2006**, and will continue until the positions are filled. Specific qualifications for appointment at the different faculty ranks can be requested in writing. Contact address: **Dr. Walter Atwood, c/o Ms. Tammy Glass, Box G-E434, 70 Ship Street, Brown University, Providence, RI 02903**. Please submit your application electronically (preferably in PDF format) to **tammy_glass@brown.edu**. Alternatively, paper copies can be mailed to the address listed above.

Brown University is an EEO/AA Employer and welcomes applications from women and minorities.

THE UNIVERSITY of WISCONSIN MADISON

The Pharmaceutical Sciences Division within The School of Pharmacy, University of Wisconsin-Madison, invites applications for ***FOUR tenure-track faculty positions*** in areas of drug discovery, drug action, and drug delivery. Applicants must have a Ph.D. or other biomedical or health sciences doctorate and demonstrate ability to establish an externally funded research program of high quality.

Successful candidates should have two-four years of postdoctoral experience and be willing to engage in productive interdisciplinary research, committed to effective teaching in undergraduate, professional, and graduate programs that serve a diverse student body, and be active in university service. Applications should consist of a cover letter including PVL# and rank, curriculum vitae, names of three references, a statement of teaching interests that includes a review of the applicant's experience in/philosophy for teaching effectively in multicultural settings, and a summary of the current and planned research.

The successful candidates will join a major university that encourages, values and supports basic, applied, and interdisciplinary research. The University of Wisconsin School of Pharmacy is vibrant and diverse, and is committed to excellence in teaching and research. Madison and its surrounding communities are consistently rated in the top tier of "most-livable cities". In addition to the energy of this Big Ten campus and a new School of Pharmacy building, Madison and South Central Wisconsin boast great schools, plentiful recreational opportunities, and year-round cultural diversions. Visit **http://www.wisc.edu/employment/madison.php** for information on living and working in Madison.

Drug Discovery: One Position at the Rank of Assistant Professor
PVL# 054770, http://www.ohr.wisc.edu/pvl/pv_054770.html

Applicants for this position should hold a Ph.D. in Chemistry or a related field and possess a strong background in organic synthesis and medicinal chemistry, and will engage in productive interdisciplinary applications of organic synthesis to drug discovery and development while working at the interface of chemistry and biology. Please contact: **Professor Richard P. Hsung, Chair, Drug Discovery Search Committee, 608-809-1063, rhsung@wisc.edu.**

Drug Action: Two Positions at the Ranks of Assistant and Associate Professor
PVL# 050727, http://www.ohr.wisc.edu/pvl/pv_050727.html

Applicants for this position must hold a Ph.D. or other biomedical or health sciences doctorate and should be exceptional biomedical scientists working in the areas of pharmacology, toxicology, neuroscience, molecular genetics, physiology, cell biology, or developmental biology. Please contact: **Professor Maureen Barr, Chair, Drug Action Search Committee, 608-265-1174; mmbarr@pharmacy.wisc.edu).**

Drug Delivery: One Position at the Rank of Assistant Professor
PVL# 054752, http://www.ohr.wisc.edu/pvl/pv_054752.html

Applicants should possess a Ph.D. in pharmaceutical sciences, biomedical sciences or biomedical engineering and engage in creative research in the areas of biopharmaceutics, pharmacokinetics or biological transport phenomena; innovative drug or gene targeting strategies; molecular imaging; or drug delivery to CNS. Please contact: **Professor Glen Kwon, Chair, Drug Delivery Search Committee, 608-265-5183; gskwon@pharmacy.wisc.edu).**

All applications must be received by **December 8, 2006** to ensure full consideration with the appointments starting on or around July 1, 2007. Please send applications to the person named for each position to **UW-Madison School of Pharmacy, 777 Highland Avenue Madison, WI 53705-2222**. If submitting by e-mail, please indicate "Application for PVL# 05. . . . " in the subject line. The search will continue until the positions are filled.

The University of Wisconsin is an Equal Opportunity/Affirmative Action Employer. Women and underrepresented minority groups are especially encouraged to apply.

CHICAGO BOTANIC GARDEN

SENIOR PLANT SCIENTIST

The Chicago Botanic Garden (CBG), in collaboration with Northwestern University, invites applications for a **SENIOR PLANT SCIENTIST** position beginning no later than September 2007. Applicants should be broadly trained in plant biology or ecology in a subfield that will complement some aspect of our current research expertise in restoration ecology, conservation biology, soil ecology, population genetics, plant systematics and economic botany. The new Senior Plant Scientist will join a team of eleven Ph.D. researchers and participate in an innovative joint Master's program in Plant Biology and Conservation with Northwestern University. We seek to appoint an individual who will take a leadership role in helping to expand the existing Master's program into a unique new doctoral program, develop a productive and creative research program, advise graduate students and interns, serve as an adjunct faculty member and teach courses in his or her area of specialty at Northwestern University.

Candidates must have a Ph.D. in biology or related discipline, a strong record of scholarship, an excellent extramural funding record for research, experience advising students at the doctoral level, and a commitment to undergraduate and graduate education. Please send a curriculum vitae, statements of research plans and teaching interests, examples of scholarly writing and three letters of reference (mailed directly from referees) by **December 15, 2006**, to: **Senior Plant Scientist Search Committee, Attn: Luanne Janikowski, Chicago Botanic Garden, 1000 Lake Cook Road, Glencoe, IL 60022** or **ljanikow@chicagobotanic.org** (electronic correspondence preferred).

CBG is situated on a 385-acre campus north of Chicago and showcases 23 different demonstration gardens as well as native areas that include woodlands, prairies and aquatic habitats, each featuring native and endangered Illinois flora (**http://www.chicagobotanic.org**).

The Chicago Botanic Garden and Northwestern University are Equal Opportunity/Affirmative Action Employers. Applications from women and minority candidates are encouraged.

BIOENGINEERING
UNIVERSITY of CALIFORNIA, BERKELEY

FACULTY POSITION

The Department of Bioengineering in the College of Engineering at the University of California, Berkeley invites applications for a **TENURE-TRACK** or **TENURED** position at the assistant, associate, or full professor level in bioengineering. The Berkeley Department of Bioengineering enjoys a close relationship with the School of Medicine at the University of California, San Francisco (UCSF). Our interdisciplinary program offers outstanding opportunities for collaboration with distinguished researchers in related departments and colleges at Berkeley, UCSF, the Lawrence Berkeley National Laboratory, and within the greater Bay Area biotech community. This exceptional environment for teaching and research in a rapidly growing field will provide the successful candidate with a unique opportunity to provide intellectual and technological leadership in bioengineering.

We seek an individual with demonstrated excellence in the field to establish an active and innovative research program in **synthetic biology and/or cellular engineering**, including technology development and applications for engineering of macromolecules, pathways, cellular systems, and multicellular systems. Exceptional candidates in other areas of bioengineering will also be given consideration. Successful applicants will be expected to teach undergraduate and graduate courses in bioengineering and should have a strong commitment to and potential for excellence in teaching and leadership. To learn more about our department please visit **http://bioeng.berkeley.edu**. The level of appointment will be based on experience and qualifications.

To apply please email a curriculum vitae with a complete list of publications; a brief description of research accomplishments; a selection of publication reprints and teaching evaluations (if available); and a brief statement of research plans and teaching interests to: BioEsearch1119@berkeley.edu. Applicants should also arrange to have at least three letters of reference sent to the department directly. Potential reviewers are referred to the Statement of Confidentiality at http://apo.chance.berkeley.edu/evalltr.html. Inquiries and/or hard copy applications and reference letters should be addressed to: Professor Adam Arkin, Search Committee Chair, Department of Bioengineering, 459 Evans Hall MC 1762, University of California, Berkeley, CA 94720-1762. The review of applications will commence on **October 31, 2006** and will continue until the position is filled. The University of California is an equal opportunity affirmative action employer, committed to excellence through diversity.

Imperial College London

Faculty of Natural Sciences
Climate Change Initiative

A Centre for Climate Change Research is being established at Imperial. The Centre will house major research programmes in the field, drawing on the College's existing world-class work across a wide spectrum of climate change related research, including atmospheric physics, atmospheric chemistry, modelling, hydrology, oceanography, paeleoclimatology, population biology and environmental policy. This represents a unique opportunity to leverage the efforts of a wide range of first class individuals to produce internationally outstanding innovative research.

Director of the Centre for Climate Change Research

As part of a major investment in the area, we are seeking to recruit a Director who will work with the senior academic staff of the College to develop and implement a coherent College wide vision for climate change research.

Applications are invited from senior figures with a proven interest in climate change and its consequences.

You will have an internationally recognised profile of excellence in research, with a substantial record of top quality publications, a sustained track record with funding bodies and a proven record of successfully managing research teams. As a Chair in Climate Change Research, you will lead your own active research programme within the Centre. You will have the breadth, vision, ability and energy to, in its initial stages, work with the Faculty Principal to develop and establish this exciting initiative and ensure its future growth and success. You would also be involved in recruitment of a number of additional posts, including:

Second Chair in Climate Change Research

Applications are invited from individuals of outstanding international reputation to establish a research team within the Centre.

Readerships and Lectureships

As part of our investment in the area, further permanent academic staff will be recruited to the Centre, including 3 readers and 5 lecturers. 2 RCUK Fellowships have also been allocated to this initiative. Each of these posts will have an appropriate Departmental affiliation

Further particulars and application details can be found at the following website:
www.imperial.ac.uk/employment/academic

More information about this initiative can be found at the following website:
www.imperial.ac.uk/climatechange

Informal enquiries are welcomed and should be directed in confidence to the Natural Sciences Faculty Principal, Professor Sir Peter Knight
p.knight@imperial.ac.uk

Closing date for applications:
17 November 2006.

Valuing diversity and committed to equality of opportunity

2006 Salary Survey

A special *Science* editorial feature

Issue date 3 November 2006

Scientists are having a pretty good year in 2006. The median scientist got a 6.4% raise this year—well above inflation—which compares favorably to the rate of our last survey in 2004.

But money, it turns out, isn't everything: Our 3rd salary survey shows that salary is just one of many things that affect how well scientists like their jobs. More important are factors—like intellectual challenge and advancement opportunities—that relate to the quality of the professional experience.

Be sure to read this special editorial feature in the **3 November issue of *Science*** and online after 3 November at **www.sciencecareers.org.**

Department of Biology and The Center for Cell and Genome Science University of Utah

The Department of Biology and the newly formed Center for Cell and Genome Science invites applications for two tenure-track faculty positions at the Assistant Professor Level. We seek creative and independent individuals working in any area of cell biology or genome science. We are particularly interested in scientists who are pursuing interdisciplinary approaches to fundamental problems in biology. Successful applicants will be expected to establish a vigorous independent research program and contribute to teaching. New faculty will have access to graduate students from programs in Biology, Molecular Biology, Biological Chemistry and Neuroscience and will be provided with outstanding infrastructural support.

Please send a curriculum vitae, representative publications and 3 letters of reference to: **Andres V. Maricq, Chair, Cell Biology/Genome Science Search Committee, Department of Biology, University of Utah, 257 South 1400 East, Salt Lake City, UT 84112-0840**. Candidates must hold a Ph.D. and/or M.D. degree(s). Review of applications will commence **December 1, 2006** and will continue until the positions are filled.

The University of Utah is an Equal Opportunity/Affirmative Action Employer and encourages applications from women and minorities and provides reasonable accommodation to the known disabilities of applicants and employees.

THE UNIVERSITY OF SOUTHERN MISSISSIPPI DEPARTMENT OF BIOLOGICAL SCIENCES

TENURE-TRACK FACULTY POSITIONS BIOINFORMATICS AND ECOINFORMATICS

The University of Southern Mississippi Department of Biological Sciences invites application for two tenure-track assistant professor positions in Computational Biology. Both positions are tied to the development of the NSF funded Mississippi Computational Biology Consortium, a network of expertise that will collectively and cooperatively interface computer science and technology with the biological sciences within the State of Mississippi. Successful candidates will be expected to establish an active, extramurally funded research program, mentor graduate students and participate in undergraduate and graduate teaching in his area of expertise. Postdoctoral research experience is required; salary is commensurate with qualifications and experience.

Bioinformatics: We seek expertise in the application of informatics tools to biological problems that enhance a growing strength in cellular and molecular biology. Suitable research areas include, but are not limited to, comparative genomics, data mining, systems biology or structural informatics. The successful candidate will have the opportunity to interact with the Mississippi Functional Genomics Network, a competitively funded NIH consortium that spans the disciplines of genomics, proteomics, cellomics and bioinformatics (**http://mfgn.usm.edu/mfgn/**). Applicants should submit a letter of application, curriculum vitae, statement of research plans, copies of pertinent reprints and three letters of reference to: **Dr. Shiao Wang, Bioinformatics Search Committee, Dept. of Biological Sciences, The University of Southern Mississippi, 118 College Drive, Hattiesburg, MS 39406-5018**. Review of applications will begin **December 1, 2006**, and continue until the position is filled.

Ecoinformatics: We also seek a colleague who uses computational techniques to study ecological processes that span large spatial and temporal scales, possibly including the ecological effects of climate change, the progress and impact of invasive species, the spread of vector borne diseases or status of threatened and endangered species. Applicants should submit a letter of application, curriculum vitae, statement of research plans, copies of pertinent reprints and three letters of reference to: **Dr. Brian Kreiser, Ecoinformatics Search Committee, Dept. of Biological Sciences, The University of Southern Mississippi, 118 College Drive, Hattiesburg, MS 39406-5018**. Review of applications will begin **December 1, 2006**, and continue until the position is filled.

The University of Southern Mississippi, a Carnegie High Research Activity Institution with over 14,000 students, is located in Hattiesburg, Mississippi, near the Gulf Coast and abundant opportunities for outdoor recreation. Hattiesburg is the medical, commercial and cultural center of south Mississippi and is ranked in the top five small metropolitan areas in the United States. The department of biological sciences is comprised of over thirty faculty and offers baccalaureate degrees in biological sciences and marine biology. Over 70 graduate students currently pursue Masters and doctoral degrees. Further information about the Department may be found at **http://www.usm.edu/biology/**. *The University of Southern Mississippi is an Affirmative Action/Equal Opportunity Employer.*

Department of Biology University of New Mexico

The Department of Biology at the University of New Mexico invites applications for an open rank full-time position, to be the first of two hires, working in the area of **cell biology**. This appointment may be at the rank of **Assistant, Associate** or **Full Professor** in a probationary status leading to a tenure decision or may be a tenured position depending on qualifications. The successful candidate will complement existing strengths in the Department, which include developmental biology, molecular biology, genomics, and molecular genetics and should be enthusiastic about working in a vigorous, broadly based biology department. The successful candidate is expected to maintain a nationally competitive, externally funded research program and participate in graduate and undergraduate teaching. Successful candidates must have a Ph.D. and preferably postdoctoral experience by the start date of the position. For complete job requirements see **http://biology.unm.edu**. To apply applicants must submit a signed letter of interest, curriculum vitae, recent reprints, statement of research and teaching interests and have at least 3 letters of recommendation sent to: **Cell Biology Search Committee, UNM Biology Department, MSC03 2020, 1 University of New Mexico, Albuquerque, NM 87131**. Review of applications will begin on **November 28, 2006**. The position will remain open until filled.

Minorities, women, veterans, and persons with disabilities are encouraged to apply. UNM is an Equal Opportunity/Affirmative Action Employer and Educator.

THE UNIVERSITY OF SOUTHERN MISSISSIPPI DEPARTMENT OF BIOLOGICAL SCIENCES

TENURE-TRACK FACULTY POSITION MICROBIOLOGY

The University of Southern Mississippi Department of Biological Sciences invites applications for a tenure-track assistant professor position in microbiology. The successful candidate will join our rapidly growing microbiology and molecular biology group. Areas of interest include, but are not limited to, pathogenic microbiology, environmental microbiology, microbial physiology, immunology and molecular biology. A competitive salary commensurate with qualifications and experience, competitive startup package, new modern lab space and state-of-the-art facilities will be provided. The successful candidate will have the opportunity to take advantage of resources provided by the Mississippi Functional Genomics Network, a competitively funded NIH consortium that spans the disciplines of genomics, proteomics, cellomics and bioinformatics (**http://mfgn.usm.edu/mfgn/**).

The University of Southern Mississippi, a Carnegie Research High Activity institution with over 14,000 students, is located in Hattiesburg, Mississippi, near the Gulf Coast and abundant opportunities for outdoor recreation. Hattiesburg is the medical, commercial and cultural center of south Mississippi and is ranked in the top five small metropolitan areas in the United States. The department of biological sciences is comprised of over thirty faculty and offers bachelor's degrees in biological sciences and marine biology. Over 70 graduate students currently pursue master's and doctoral degrees and specialize in microbiology, molecular biology, environmental biology or marine biology. Further information about the department of biological sciences may be found at **http://www.usm.edu/biology/**.

The successful candidate will be expected to establish an active, extramurally funded research program, mentor graduate students and participate in undergraduate and graduate teaching in his area of expertise. A doctorate in appropriate discipline and postdoctoral research experience is required.

Applicants should submit a letter of application, curriculum vitae, statement of research plans, copies of pertinent reprints and three letters of reference to: **Dr. Mohamed Elasri, Microbiology Search Committee, Dept. of Biological Sciences, The University of Southern Mississippi, 118 College Drive # 5018, Hattiesburg, MS 39406-0001**. Review of applications will begin **December 1, 2006**, and continue until the position is filled.

The University of Southern Mississippi is an Affirmative Action/Equal Opportunity Employer/ Americans with Disabilities Act Institution.

SLOAN-KETTERING INSTITUTE CELL BIOLOGY PROGRAM
Tenure-Track Faculty Positions

The Cell Biology Program, Sloan-Kettering Institute (www.ski.edu) has initiated a search for tenure-track faculty members. We are interested in outstanding individuals who have the potential to develop an innovative, independent research program that complements and enhances our existing strengths. Candidates with research interests in exciting areas of eukaryotic cell biology and using a variety of experimental approaches and systems are encouraged to apply. New faculty will be eligible for appointment in the recently established Gerstner Sloan-Kettering Graduate School of Biomedical Sciences as well as the Weill Graduate School of Medical Sciences of Cornell University. Sloan-Kettering has an outstanding infrastructure and state of the art core resources. The new 23-story Zuckerman Research Center opened earlier this year and will allow significant expansion of our research programs.

Candidates should e-mail their application in PDF format to **cellbio@mskcc.org** by November 17, 2006. The application should include a Curriculum Vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three letters of reference sent by e-mail to **cellbio@mskcc.org** and by regular mail to **Cell Biology Search, c/o Mrs. Stephanie Miranda, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 428, New York, NY 10021.** The letters should arrive by November 17, 2006. Inquiries may be sent to Mrs. Miranda or to Dr. Alan Hall, Chair, Cell Biology Program, Sloan-Kettering Institute, at the addresses listed above. Memorial Sloan-Kettering Cancer Center is an Equal Opportunity Employer.

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.
www.mskcc.org

Ultrafast Staff Physicists

Lawrence Berkeley National Laboratory (LBNL) is a world leader in science and engineering research, with 11 Nobel Prize recipients over the past 75 years, and 59 present members of the National Academy of Science. LBNL conducts unclassified research across a wide range of scientific disciplines, hosts four national user facilities, and has strong ties to the faculty and students at the University of California's Berkeley campus.

The LBNL Materials Sciences Division seeks to hire two Staff Scientists in the area of ultrafast materials research. The candidates will join the Ultrafast Materials Science Center and are expected to formulate and conduct an independent research program on fundamental dynamics in complex materials, correlated electron systems, nanostructures, and novel systems using advanced ultrafast spectroscopy techniques ranging from THz, infrared, visible, and x-ray pulses, to photoelectron/photoemission spectroscopy. The emphasis is on using time-domain approaches to provide new understanding of complex behavior, emergent phenomena, and exotic properties in condensed matter.

The candidates will work with other LBNL investigators (and U.C. Berkeley faculty) and ongoing programs in ultrafast materials research. Unique LBNL facilities include state-of-the-art femtosecond lasers, THz sources, high harmonic sources, femtosecond x-ray beamlines at the Advanced Light Source, and other national user facilities. Requirements include extensive knowledge of condensed matter physics and/or physical chemistry, a strong record of research beyond the Ph.D., and experience with ultrafast lasers and measurement techniques.

Two positions are available: one career (**#019423**) and one term (**#019490**). The career position requires considerable experience and demonstrated ability to formulate and conduct an independent research program at the international level. The term position is for a less experienced candidate, with intellectual initiative and creativity. Please provide a CV, list of publications, statement of research interests, and five references. Please submit all materials online (**http://jobs.lbl.gov**) as one document and reference the specific job#, and "Journal/Magazine" and "Science Magazine" as your source.

LBNL is an Affirmative Action/Equal Opportunity Employer committed to the development of a safe and diverse workforce. **www.lbl.gov**

Department Head and Professor Biochemistry and Molecular Biology Oklahoma State University

EXTENDED SEARCH

The Biochemistry and Molecular Biology Department is accepting applications from exceptional candidates for Department Head and Professor. The Department Head will provide leadership for education and research, maintain an independent research program, and serve as administrative liaison to the Division of Agricultural Sciences and Natural Resources, the University, and outside agencies.

The successful applicant will have a Ph.D. in Biochemistry, Molecular Biology, or a related field and have an outstanding record of scholarly achievement. The candidate should have qualifications commensurate with appointment as a full Professor and evidence of ability to lead a nationally competitive program. The Department emphasizes structural biology and gene regulation, and has excellent extramural support. The new Department Head will have the opportunity to lead departmental growth initiatives and promote Oklahoma agricultural science through existing programs in animal and plant research. Additionally, he/she will maintain a commitment to teaching and professional development of undergraduate and graduate students.

Oklahoma State University is a comprehensive, public, four-year, nationally accredited university located in Stillwater, Oklahoma. Stillwater provides exceptional quality of life in a college community, one hour from Oklahoma's two largest cities. Visit **http://biochem4.okstate.edu** for more information. Review of applicants will begin **December 1, 2006**, and the position is to be filled by July 1, 2007, or soon thereafter. Send applications in confidence to: **BMB Department Head Search Committee, c/o Ms. Sue Bonner, Division of Agricultural Sciences and Natural Resources, 235 Ag Hall, Oklahoma State University, Stillwater, OK. 74078-6022**. For additional information, please contact **Ms. Sue Bonner** at **(405) 744-5524**, or **facsimile: (405) 744-8863**.

Oklahoma State University is an Affirmative Action/Equal Opportunity Employer committed to Multicultural Diversity.

University of Michigan
Center for stem cell biology
life sciences institute

The Life Sciences Institute and the University of Michigan Medical School invite applications for tenure track **ASSISTANT PROFESSOR** positions. We are seeking outstanding scholars, with Ph.D., M.D. or equivalent degrees and relevant postdoctoral experience, who show exceptional potential to develop an independent research program that will address fundamental issues in any aspect of stem cell biology. Applicants who have already established successful independent research programs will be considered for tenured **ASSOCIATE PROFESSOR** or **PROFESSOR** positions.

Applicants should send a curriculum vitae, copies of up to three reprints, a one- to two-page summary of research plans, and arrange to have three letters of reference sent directly by November 1, 2006 to: **Stem Cell Search Committee, c/o Rebecca Fritts, Life Sciences Institute, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, Michigan, 48109-2216**.

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.

POSITIONS OPEN

ASSISTANT PROFESSOR/ MICROBIOLOGIST/ECOLOGIST
Department of Biology
Ball State University
Muncie, Indiana

Tenure-track position available August 17, 2007. Responsibilities: teaching undergraduate and graduate courses in microbiology for allied health sciences, general ecology, and aquatic microbiology; development of a research program involving undergraduate and graduate students and grant procurement; providing service to the academic community. Minimum qualifications: earned doctorate in a biological or environmental science by November 1, 2007; effective written and oral communication skills; commitment to excellence in teaching; competency in current approaches in environmental microbiology. Preferred qualifications: demonstrated teaching ability and publications and/or evidence of other scholarly activity.

Send letter of application, curriculum vitae, documentation of scholarly activity and teaching ability (e.g., student and peer review evaluation summaries), copies of transcripts, and three letters of reference to: **Dr. John McKillip, Chair, Microbiologist Search Committee, Department of Biology, Ball State University, Muncie, IN 47306. (Website: http://www.bsu.edu)** To be assured of full consideration, all application materials should be received by November 21, 2006.

Ball State University is an Equal Opportunity, Affirmative Action Employer and is strongly and actively committed to diversity within its community.

ASSISTANT PROFESSOR IN BEHAVIORAL/MATHEMATICAL GENETICS

The Institute for Behavioral Genetics at the University of Colorado, Boulder, seeks to build additional expertise in mathematical/statistical genetics. We invite applications for a Tenure-Track position with a joint appointment in an appropriate academic department. Preference will be given to candidates with an active research program involving the development of mathematical genetics methods that can be applied to the study of behavioral traits. The appointee will participate in the research and teaching missions of both the Institute and his or her academic department. Minimum requirements are a Ph.D., M.D., or equivalent degree. Applicants should submit curriculum vitae, a statement of research and teaching interests, sample research papers, and at least three letters of recommendation to: **Search Committee (Faculty), Institute for Behavioral Genetics, University of Colorado, 447 UCB, Boulder, CO 80309-0447.** Inquiries should be addressed to: **Michael Stallings, Search Committee Chair, telephone: 303-492-2826,** or **e-mail: michael.stallings@colorado.edu.** Application review will begin December 1, 2006, and the position will remain open until filled. The appointment is expected to begin August 2007. *The University of Colorado at Boulder is committed to diversity and equality in education and employment.*

POSTDOCTORAL POSITION, Lyme disease pathogenesis. A Postdoctoral Position is available to study gene regulation and regulatory networks governing virulence expression by *Borrelia burgdorferi* (*Proc. Natl. Acad. Sci.* **98:**12724, 2001, **99:**1562, 2002, **100:**11001, 2003, and **102:**6972, 2005; *Journal of Experimental Medicine* **199:**641, 2004). The position offers the opportunity to carry out research in an attractive, dynamic research environment with outstanding resources. Candidates should have a Ph.D. with a background in bacterial pathogenesis, molecular biology, and bacterial genetics. Please provide curriculum vitae and the names and addresses of three references to: **Dr. Michael V. Norgard, Chair, Department of Microbiology, University of Texas Southwestern Medical Center, 6000 Harry Hines Boulevard, Dallas, TX 75390-9048. (E-mail: michael.norgard@utsouthwestern.edu.)** *University of Texas Southwestern Medical Center is an Equal Opportunity Employer.*

POSITIONS OPEN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

POLICY ANALYST

The United Network for Organ Sharing (UNOS) in Richmond, Virginia, seeks a Policy Analyst (PA). Must have graduate degree in health policy, public policy, public health, or a related field. Responsibilities include support of national transplantation policy development, including allocation policy for the national Organ Procurement and Transplantation Network (OPTN), operated by UNOS for 20 years under contract with the federal Department of Health and Human Services. PA will facilitate operation of national committee system that develops transplant policy; help conceptualize and plan policy analyses; manage tasks within OPTN policy development process; interpret and report transplant data analyses; and serve as liaison to national committees of medical professionals, transplant patients, and donor family members. A full position description is available at **website: http://www.unos.org.** Please submit resume and/or curriculum vitae to **e-mail: employment@unos.org** or **Human Resources, United Network for Organ Sharing, P. O. Box 2484, Richmond, VA 23218.** *Minorities encouraged to apply. Equal Opportunity Employer.*

TWO TENURE-TRACK POSITIONS
Department of Biology, Texas Woman's University (TWU)

ASSISTANT PROFESSOR, computational biology. Requires a Ph.D. and postdoctoral experience in biological sciences/computational biology. The successful candidate will teach undergraduate/graduate courses, and develop an externally funded interdisciplinary research program in bioinformatics/computational biology. **Search Committee Chair: Dr. DiAnna Hynds (telephone: 940-898-2359, e-mail: dhynds@twu.edu).**

ASSISTANT/ASSOCIATE PROFESSOR, science education. Requires a Ph.D. in science education or biological sciences (postdoctoral experience desirable). The successful candidate will provide leadership in the teacher education program, teach undergraduate/graduate courses, supervise student teachers, and develop an externally funded teacher training program. **Search Committee Chair: Dr. Camelia Maier (telephone: 940-898-2358, e-mail: cmaier@twu.edu).**

To apply send a letter of interest, curriculum vitae, brief description of research and teaching interests, and the names and contact information for three references to the appropriate **Search Committee Chair** at: **P.O. Box 425799, Denton, TX 76204-5799; fax: 940-898-2382; website: http://www.twu.edu/as/bio.**

Review of applications will begin immediately and continue until positions are filled.

TWU is an Affirmative Action/Equal Opportunity Employer.

POSTDOCTORAL POSITION. A Postdoctoral Position funded by the National Institutes of Health is available, to study the roles of insulin, nitric oxide, and protein tyrosine phosphatases in regulation of vascular smooth muscle cell signaling and neointima formation in vascular injury. Our projects address important basic science questions and also have relevance to clinical problems. Experience in molecular biology and/or rat and mouse surgery is essential. Competitive salary is offered. Please send curriculum vitae and the names of three references to: **Dr. Aviv Hassid, Department of Physiology, University of Tennessee, 894 Union Avenue, Memphis TN 38163. E-mail: ahassid@tennessee.edu, fax: 901-448-7126.** *The University of Tennessee is an Equal Employment Opportunity/Affirmative Action Title VI/Title IX/Section 504/ADA/ADEA Institution in the provision of its education and employment programs and services.*

POSITIONS OPEN

The Department of Chemistry and Biochemistry at the University of Oklahoma invites applications for a tenure-track faculty position in physical and/or inorganic chemistry at the rank of **ASSISTANT PROFESSOR.** Applicants must have completed a Ph.D. degree in chemistry, biochemistry, or closely related area by the beginning of the appointment, August 16, 2007. We are seeking individuals with research programs in any area of physical and/or inorganic chemistry, and we are especially interested in candidates who will contribute to University-wide initiatives in the integrative life sciences or nanoscience. The candidates will be expected to contribute to our teaching programs at both the undergraduate and graduate levels particularly in the areas of physical and/or inorganic chemistry. Interested individuals should submit curriculum vitae, a detailed description of their research plans, and a statement of their teaching interests and philosophy. Candidates should request three letters of recommendation and have them sent directly to: **Professor Wai Tak Yip, Chair of Faculty Search Committee, Department of Chemistry and Biochemistry, 620 Parrington Oval, Norman, OK 73019.** We also will accept completed applications, in PDF format, sent to **e-mail: sgfisher@ou.edu.** Review of applications will begin on November 15, 2006, and will continue until the position is filled. *Minorities and women are especially encouraged to apply. The University of Oklahoma is an Affirmative Action/Equal Opportunity Employer and is responsive to the needs of dual-career couples.*

California State University, Sacramento, is seeking one new tenure-track faculty member in environmental studies with expertise in environmental science, or environmental science and policy. Appointment will be at a probationary, entry-level tenure-track with the rank of **ASSISTANT PROFESSOR,** beginning fall 2007. Qualifications include: completion of the Ph.D. in a science field appropriate to an interdisciplinary program in environmental studies by January 3, 2008; demonstrated commitment to teaching; demonstrated research experience, including familiarity with quantitative environmental studies. Experience dealing with the role of environmental science in environmental policy is preferred; knowledge of science issues in environmental conflicts in the Sacramento region also desirable. The ability to address the needs of diverse populations is highly desirable. Submit letter of application, curriculum vitae, telephone numbers of at least three references who will speak to the professional qualifications of the applicant, and a statement of teaching and scholarly interests to: **Dudley Burton, Department of Environmental Studies, California State University, 6000 J Street, Sacramento, CA 95819-6001.** Review of applications begins December 15, 2006. Position open until filled. Further information at **website: http://csus.edu/ssis.** *Sacramento State is an Affirmative Action/Equal Opportunity Employer.*

The State University of New York (SUNY), Potsdam, invites applications for a tenure-track position as **ASSISTANT PROFESSOR** of biology for fall 2007. Qualifications include: (1) a Ph.D. in the biological sciences, (2) a strong, demonstrable commitment to excellence in undergraduate teaching and learning, and (3) the ability to establish an ongoing research program involving undergraduates. Teaching responsibilities may include general microbiology, an additional upper-division microbiology course, nonmajors biology courses as well as the teaching of the general biology lecture and/or laboratories. Submit a letter of application, curriculum vitae, description of teaching and research interests, documentation of excellence in teaching, unofficial transcripts, and the names and contact information of three references to: **Dr. Laura Rhoads, Department of Biology, State University of New York, Potsdam, NY 13676.** For full consideration, applications should be received by 15 December 2006. For more information on the Department of Biology and a more detailed job description visit **website: http://www.potsdam.edu/BIOL/.** SUNY *Potsdam is an Equal Opportunity Employer committed to excellence through diversity.*

Southern Illinois University School of Medicine

Visit us on the web at www.siumed.edu

TWO TENURE-TRACK FACULTY POSITIONS ASSISTANT/ASSOCIATE PROFESSORS VIROLOGY AND VIRAL ONCOLOGY

The Department of Medical Microbiology, Immunology, and Cell Biology (MMICB) of Southern Illinois University School of Medicine - Springfield and SimmonsCooper Cancer Institute jointly invite applications for two full-time tenure-track appointments at the Assistant or Associate Professor level in Virology. We seek a candidate with general virology interests and a second focused on viral oncology. Successful candidates will join a growing, highly interactive and collegial group of 12 well-funded investigators within the MMICB department located in newly-built state-of-the-art research facilities. New faculty with a focus on viral oncology will be cross-appointed to the SIU SimmonsCooper Cancer Institute. Faculty will have access to campus and Cancer Institute core resources including confocal, electron, and laser-capture microdissection microscopy, microarray facilities, flow cytometry, luminex, tumor tissue bank, AAALAC certified animal facilities, and a new BSL-3 facility.

Candidates must have a Ph.D. and/or M.D. degree with training in molecular virology and/or viral oncogenesis. Our interests include but are not limited to viral immunity, trafficking, pathogenesis, vaccine biology and/or development, molecular oncogenesis, genetics, signal transduction, and translational oncology. Candidates at the Assistant Professor level should show evidence of productive accomplishments and ability to pursue an independent research program. Candidates at the Associate Professor level must have a currently funded research program and a track record of national funding. Successful candidates will receive competitive salaries, attractive start-up packages and are expected to develop and maintain an externally funded research program and teach at the medical and graduate levels.

Interested applicants should submit their curriculum vitae, description of current and future research plans, copies of 3 recent representative publications, and contact information for at least three references in an electronic form (PDF preferred) by email to **breichert@siumed.edu** with 'virology applicant' indicated in the subject line. Hard copies may be sent to:

Chair of Virology Search Committee
Southern Illinois University
School of Medicine
P.O. Box 19626
Springfield, IL 62794-9626
http://www.siumed.edu/mmi/

Applications must be received by **December 15, 2006**, but review will begin immediately.

SIU School of Medicine is an EO/AA Employer.

FACULTY POSITIONS

Department of Molecular Medicine - 05997

Located in Ithaca, N.Y., Cornell University is a bold, innovative, inclusive and dynamic teaching and research university where staff, faculty, and students alike are challenged to make an enduring contribution to the betterment of humanity.

Job Description: The Department of Molecular Medicine invites applications for tenure-track faculty positions at the level of Assistant Professor or higher. These positions are part of a diverse campus-wide expansion under the New Life Sciences Initiative. (lifesciences.cornell.edu/about/initiative.php) To strengthen our current departmental research programs, (www.vet.cornell.edu/molecular/), we seek candidates studying signal transduction by molecular, cellular, biochemical, physical, or other contemporary approaches. We are particularly interested in candidates who use innovative and interdisciplinary approaches and who study the basic signaling mechanisms relevant to cancer or other disease processes. Successful candidates are expected to develop a strong and independent research program and contribute to the teaching activities of the Department. Salary and rank will be competitive and commensurate with qualifications and experience.

Qualifications: Candidates should have a Ph.D., DVM, M.D., or equivalent degree, be firmly committed to an academic career, have a track record of excellence in research, and an outstanding or potentially outstanding research program.

Please submit a curriculum vitae and a description of current and future research interests as a single PDF file to: Search Committee Chair c/o: **dac20@cornell.edu**.

Arrange for three letters of recommendation to be sent both electronically and in hard copy to:

Search Committee Chair, Department of Molecular Medicine
College of Veterinary Medicine
Cornell University
Ithaca NY 14853-6401

Review of applications will begin November 1, 2006 and will continue until the positions are filled. Women and minorities are strongly encouraged to apply.

Cornell University

Cornell University is an Affirmative Action, Equal Opportunity Employer and Educator.

http://chronicle.com/jobs/profiles/2377.htm

F A I R F I E L D U N I V E R S I T Y

Tenure Track Assistant Professorship

The Department of Mathematics and Computer Science at Fairfield University invites applications for a tenure track assistant professorship to begin in September 2007. We are looking for candidates whose research specialty is in biological mathematics, including, but not limited to, Biostatistics, Bioinformatics, Computational Biology, and Systems Biology. A doctorate in mathematics is required. Strong evidence of research potential, demonstrated success in classroom instruction, and a solid commitment to teaching are essential. Interest in issues related to the advancement of underrepresented groups in mathematics and the sciences is an important consideration.

One third of the successful candidate's teaching load will consist of courses listed under or cross-listed with the Department of Biology, including, possibly, an upper level course in the candidate's areas of expertise.

Fairfield University is a comprehensive Jesuit university with about 3,300 undergraduates and a strong emphasis on liberal arts education. The Department of Mathematics and Computer Science consists of 14 full-time faculty members. The department offers a BS and an MS in mathematics. The teaching load is 3 courses/9 credit hours per semester. Fairfield offers competitive salaries and benefits. The picturesque campus is located on Long Island Sound in southwestern Connecticut, about 50 miles from New York City. Fairfield is an Affirmative Action/Equal Opportunity Employer. For further details see http://cs.fairfield.edu/mathhire. Applicants should send a letter of application, a curriculum vitae, teaching and research statements, and three letters of recommendation commenting on the applicant's experience and promise as a teacher and scholar, to **Matt Coleman, Chair of the Department of Mathematics and Computer Science, Fairfield University, Fairfield CT 06824-5195**. *Full consideration will be given to complete applications received by January 15, 2007.* Please let us know whether you will be attending the AMS/MAA Joint Meetings in New Orleans in January.

Fairfield UNIVERSITY

Jesuit. Personal. Powerful.

Visit our website at www.fairfield.edu

POSITIONS OPEN

ASSISTANT PROFESSOR, MAMMALIAN DEVELOPMENTAL GENETICS. The Biochemistry and Cellular and Molecular Biology (BCMB) Department at the University of Tennessee seeks to fill a tenure-track faculty position at the Assistant Professor level to begin in August 2007. We will particularly welcome applications from individuals who apply genomic or proteomic methods and/or use mouse genetic models to address problems in developmental biology, and from individuals with interests in developmental neurobiology, but outstanding applications from individuals in all areas of developmental genetics will be considered. The successful candidate for this position will benefit from interactions with strong research groups within the BCMB Department and in other units on campus and at the nearby Oak Ridge National Laboratory in neurobiology, chromatin and chromosome dynamics, biology of cancer and aging, cell division and cell cycle, structural biology, enzyme mechanisms, mouse genetics/genomics, proteomics and computational biology. The successful applicant will be expected to develop an independent, externally funded research program in mammalian developmental genetics, to provide state-of-the-art training for graduate students and postdoctoral researchers, and to contribute to the teaching mission of the BCMB Department at both the undergraduate and graduate levels. Required qualifications include a Ph.D. and postdoctoral experience in relevant areas of biology, evidence of significant scientific productivity, and a commitment to an integrated program of teaching and research. The University welcomes and honors people of all races, creeds, cultures, and sexual orientations, and values intellectual curiosity, pursuit of knowledge, and academic freedom and integrity.

Interested candidates should send a cover letter, a resume, a description of research experience and of the proposed research program, and the names of three individuals who can provide letters of reference to: **Bruce McKee, Head, Biochemistry and Cellular and Molecular Biology Department, M407 WLS, University of Tennessee, Knoxville, TN 37996-0840.** Review of applications will begin on November 1, 2006, and continue until the position is filled.

The University of Tennessee is an Equal Employment Opportunity/Affirmative Action/Title VI/Title IX/Section 504/ADA/ADEA Institution in the provision of its education and employment programs and services.

SOUTHERN ILLINOIS UNIVERSITY
Edwardsville

The School of Pharmacy invites applications for a 12-month tenure-track position at the rank of **ASSISTANT, ASSOCIATE, or FULL PROFESSOR.** A Ph.D. in pharmacology or a closely related area is required. Individuals having previous teaching experience and postdoctoral training are preferred. The successful candidate will be expected to demonstrate excellence in teaching in the professional (Pharm.D.) program and to establish independent and/or collaborative research. Applicants with expertise in molecular, cellular, and/or analytical approaches related to pharmacology/toxicology are encouraged to apply. Opportunities for research collaborations exist on the Southern Illinois University Edwardsville (SIUE) campus and with the SIU Schools of Dental Medicine and Medicine. Additionally, the proximity of the SIUE School of Pharmacy to numerous educational institutions and pharmaceutical and biotechnology firms in the St. Louis metropolitan area provides for a stimulating intellectual environment. The review of applications will begin immediately and continue until the position is filled. The starting date is negotiable. To be considered for this position, applicants should submit a letter of application, curriculum vitae, and the names and addresses of three references to: **Michael Crider, Chair, Department of Pharmaceutical Sciences, Southern Illinois University Edwardsville, Edwardsville, IL 62026-2000. E-mail: mcrider@siue.edu. Telephone: 618-650-5162.** *SIUE is a state University; benefits to state-sponsored plans may not be available to holders of F1 or J1 visas. SIUE is an Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

ASSISTANT PROFESSOR
Molecular Microbiology

The Department of Molecular Biology at the University of Wyoming seeks an outstanding scientist for a tenure-track position at the Assistant Professor level. We seek an interactive colleague who uses molecular approaches to address important problems in microbiology. We are particularly interested in candidates investigating molecular and cellular mechanisms of microbial pathogenesis and host-pathogen interactions. However, demonstrated excellence in research is more important than specific area. The successful candidate will be part of the Microbiology Program that integrates Microbiologists across departmental and college boundaries. The candidate will be expected to establish an extramurally funded research program and participate in undergraduate teaching of general or medical microbiology, as well as contribute to the Molecular and Cellular Life Sciences Graduate Program **(website: http://www.uwyo.edu/mcls/).** Salary and startup package will be competitive. Candidates must have a Ph.D. degree and evidence of productive postdoctoral experience. The applications should be sent to **e-mail: uwmbio@uwyo.edu** formatted as a single PDF file containing a cover letter, curriculum vitae, research plans, and teaching philosophy. Three letters of recommendation should be sent to **e-mail: uwmbio@uwyo.edu** or to: **Chair, Microbiology Search Committee, Department of Molecular Biology, University of Wyoming, 1000 E. University Avenue, Department 3944, Laramie, WY 82071.** The Department of Molecular Biology consists of 14 faculty members with diverse research interests and significant extramural support. The University enrolls 12,000 students including approximately 2,500 graduate students. Laramie is located in the Rocky Mountains area of southeastern Wyoming, 120 miles from Denver, Colorado. For additional information see **website: http://uwacadweb.uwyo.edu/UWmolecbio/.** Screening of applications will begin on November 15, 2006, and continue until a suitable candidate is identified. *The University of Wyoming is an Equal Opportunity /Affirmative Action Employer.*

ASSISTANT/ASSOCIATE PROFESSOR OF APPLIED MATHEMATICS

The Science Programs at the Vancouver Campus and the Mathematics Department of Washington State University (WSU) invite applications for a full-time, tenure-track Assistant or Associate Professor position in applied mathematics located in Vancouver. The successful candidate will be a dynamic and collaborative individual who uses mathematical techniques to study biological and/or environmental problems. Area of specialization is open but exceptional scholars who complement the strengths of existing science faculty are encouraged to apply. Applicants must have a Ph.D. in mathematics or a closely related field by date of hire and demonstrate high potential to establish an externally funded research program that includes mentoring diverse graduate and undergraduate students. The successful candidate will have demonstrated the ability to teach undergraduate and graduate courses. WSU Vancouver offers undergraduate and graduate programs and is expected to double its student body and faculty in the coming years. WSU Vancouver is located across the Columbia River from Portland, Oregon, and offers significant opportunities for research and an excellent quality of life. For additional information, see **website: http://www.vancouver.wsu.edu/programs/sci/.**

Applicants should submit curriculum vitae, copies of two publications, a statement of teaching philosophy and interests, research accomplishments, and three letters of reference to: **Brian Tissot, Chair, Applied Mathematics Search, Washington State University Vancouver, 14204 N.E. Salmon Creek Avenue, Vancouver, WA 98686-9600.** Review of completed applications will begin on November 22, 2006.

Washington State University is an Equal Opportunity/Affirmative Action Educator and Employer. Members of groups historically underrepresented in mathematics are strongly encouraged to apply.

POSITIONS OPEN

FACULTY POSITIONS IN IMMUNOLOGY
Department of Microbiology-Immunology and Interdepartmental Immunobiology Center
Northwestern University
Feinberg School of Medicine

A tenure-track position is open for a full-time faculty researcher (Ph.D., M.D./Ph.D. or M.D.) in the areas of innate immunity, immune development, immune regulation, or immunobiology of autoimmune or infectious diseases. Rank is open, and salary is negotiable. All applicants should have substantial peer-reviewed publications that demonstrate research productivity and the ability to perform cutting-edge research. Candidates for an **ASSISTANT PROFESSOR** position should have postdoctoral research experience. Persons seeking appointment as **ASSOCIATE or FULL PROFESSOR** should have substantial, long-term research productivity and a history of grant support and academic service. Candidates should have an interest in teaching graduate and medical students. Starting date is negotiable after September 1, 2007. Application materials will be reviewed as received, but to receive full consideration, should be received by February 1, 2007. Please send a complete curriculum vitae and the name and contact information of at least three references by e-mail to **e-mail: immunosearch@northwestern.edu.**

Northwestern University is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

The Department of Biological Sciences at Le Moyne College seeks two tenure-track **ASSISTANT PROFESSORS** in (1) molecular genetics, and (2) developmental biology to begin August 2007. Teaching responsibilities will include courses in genetics and bioinformatics (position 1), developmental biology (position 2), and upper-level courses in applicants' areas of expertise; ability to teach in introductory or nonmajors courses essential. Additional responsibilities for both positions include advising biology majors and implementing a research program that encourages undergraduate participation. Applicants must have a Ph.D.; undergraduate teaching experience preferred. A letter of application (indicating position sought) with curriculum vitae, transcripts, three letters of recommendation, and separate statements of teaching philosophy and research interests should be submitted electronically to **e-mail: lemoynehr@lemoyne.edu** with a subject line of either bio-genetics, or bio-development. Review of applications will begin November 17, 2006, and continue until the position is filled. Visit our webpage at **website: http://www.lemoyne.edu.**

Le Moyne College is an Equal Opportunity Employer and encourages women, persons of color, and Jesuits to apply.

Pending final budgetary approval, Drake University invites applications for a full-time, tenure-track position as **ASSISTANT PROFESSOR** of microbiology/virology, starting fall semester 2007. Ph.D. with postdoctoral experience desirable. Teaching responsibilities include microbiology for pharmacy students, virology, environmental health, and a course in the candidate's specialty. A commitment to teaching and undergraduate research in an interdisciplinary setting is expected, along with the potential for attracting externally funded research. Send letter of application, curriculum vitae, e-mail addresses of three references, philosophical statement of teaching and research, publication sample, and transcripts to: **Richard Wacha, Chair, Department of Biology, Drake University, 2507 University Avenue, Des Moines, IA 50311.** E-mail inquires and electronic submissions to **e-mail: richard.wacha@drake.edu.** Review of applications begins November 10, 2006, and will continue until the position is filled. *Drake University is an Equal Opportunity Employer and actively seeks applicants who reflect the diversity of the nation. No applicant shall be discriminated against on the basis of race, color, national origin, creed, religion, age, disability, sex, gender identity, sexual orientation, or veteran status.*

State University of New York

Upstate Medical University

ASSISTANT/ASSOCIATE PROFESSOR DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

We seek applications to fill TWO tenure-track positions at either the Assistant or Associate Professor levels from individuals studying fundamental molecular processes in eukaryotic organisms. The successful applicants will be expected to develop well-funded research programs and to contribute to medical and graduate teaching. We offer a highly competitive start-up package and salary. Further information about the department can be found at: **www.upstate.edu/biochem**.

Candidates should have a Ph.D. or equivalent, postdoctoral experience and a strong publication record. Applicants should email a pdf file containing a curriculum vitae, a summary of research accomplishments and future research plans to **Biochem@upstate.edu**. In addition, three letters of reference should be mailed directly to: **Dr. Barry E. Knox, Search Committee Chair, Department of Biochemistry and Molecular Biology, 750 East Adams Street, Syracuse, NY 13210**. Review of applications will begin on **November 1, 2006** and continue until the position is filled.

Women and minorities are highly encouraged to apply. Upstate Medical University is an Equal Opportunity/Affirmative Action Employer.

Berkeley Lab — 75 Years of World-Class Science 1931-2006

Scientist or Staff Scientist

Lawrence Berkeley National Laboratory (LBNL) is located in the San Francisco Bay Area on a 200-acre site in the hills above the University of California's Berkeley campus and is managed by the University of California. A leader in science and engineering research for more than 75 years, LBNL is the oldest of the U.S. Department of Energy's National Laboratories.

NOTE: This career position will be hired at either the Scientist or Staff Scientist level, depending on qualifications and experience.

Reporting to the Division Deputy for Experimental Systems of the Advanced Light Source (ALS), the Staff Scientist functions as an experimental physicist engaged in the development of imaging based on coherent soft x-ray scattering.

Responsibilities: The candidate will lead the ALS efforts in imaging based on coherent soft x-ray scattering, including development of the research program, support of the ALS user community, and development of beamline and end station instrumentation. He/she will develop their own scientific program based on coherent soft x-ray scattering, and where synergy exists, investigate the use of FEL sources where applications demand higher pulse intensities.

It will be necessary to disseminate research results via publications in peer reviewed journals and present results via verbal presentations at various meetings including conferences and peer reviews of projects. The candidate must perform work with knowledge and understanding of laboratory safety practices and policies.

Qualifications: A Ph.D. or equivalent experience in the physical sciences or engineering is required for the position, in addition to demonstrated leadership in the field of imaging based on coherent soft x-ray scattering. Extensive experience of synchrotron radiation research, including knowledge of the operation and characteristics of undulator sources, beamlines, and detectors is essential. The candidate must have proven ability to work in innovative R&D projects involving sophisticated instrumentation, as well as demonstrated experience and ability to work effectively with a multidisciplinary team of physicists, engineers, technical support staff, and collaborating scientists. He/she will also need an excellent scientific publishing record in the field of coherent soft x-ray scattering, and excellent verbal and written communication skills.

For fastest consideration, apply online at: **http://jobs.lbl.gov**, select "Search Jobs", and enter 019483 in the keyword search field. Enter "Science Magazine" as your source.

LBNL is an Affirmative Action/Equal Opportunity Employer committed to the development of a diverse workforce.

For more information about LBNL and its programs, **visit www.lbl.gov**.

USF UNIVERSITY OF SOUTH FLORIDA

Assistant Professors in Ecology

The Department of Biology, Division of Integrative Biology at the University of South Florida invites applications for two tenure track positions in Ecology to begin in Fall 2007. We are especially interested in candidates whose work is focused in one of the following three areas: **Quantitative Ecology**, with a research emphasis in mathematical or statistical models; **Molecular Ecology**, with a research emphasis at the interface of ecology and evolution at any level, from organisms to ecosystems; or **Physiological Ecology**, with a research emphasis on the responses of organisms to environmental stressors or changing environmental conditions. The Tampa Bay area has ready access to a variety of marine, freshwater and terrestrial habitats in a sub-tropical environment. USF has been designated as a university with very high research by the Carnegie Foundation for the Advancement of Teaching.

Faculty whose research complements existing strengths in the new Division of Integrative Biology are encouraged to apply (see: **http://www.cas.usf.edu/biology**). A Ph.D. in Biology or related field is required and post-doctoral experience is preferred. Evidence of potential to develop a strong externally funded research program is desirable. Salary is negotiable. Applicants should submit a curriculum vitae, statements of research and teaching interests, three representative publications and arrange to have three letters of recommendation sent to the **Ecology Search Committee, Division of Integrative Biology, Department of Biology SCA 110, University of South Florida, 4202 East Fowler Avenue, Tampa, FL 33620**. Review of applications will begin on **December 1, 2006** and continue until the position is filled. According to Florida Law, applications and meetings regarding them are open to the public. For ADA accommodations, please contact **Janet Gauthier** at **(813) 974-3250** five working days prior to need.

USF is an AA/EEO Institution.
Women and minorities are encouraged to apply.

DUQUESNE UNIVERSITY

BIOLOGICAL SCIENCES FACULTY

Duquesne University invites applications for a tenure-track position in the Department of Biological Sciences. The successful applicant is expected to develop a vigorous independent research program involving the study of molecular, cellular, and/or organismal processes. Areas of interest include, but are not limited to, cell biology, development, immunology, and physiology.

The successful candidate will join an active department of 17 faculty members with a commitment to combining externally funded research with excellence in teaching at both the graduate and undergraduate levels. Applicants must have post-doctoral experience, and are expected to mentor MS and PhD students. Preference will be given to candidates at the Assistant Professor level; however, more senior candidates may also be considered. Competitive salary and start-up packages are available. Additional information about the Department can be found at **http://www.science.duq.edu/biology**.

To apply, send a cover letter, CV, statements of research and teaching goals, and three letters of recommendation to Dr. Michael Jensen-Seaman, Biology Faculty Search Committee, Department of Biological Sciences, 201 Mellon Hall, 600 Forbes Avenue, Pittsburgh, PA 15282. Review of applications will begin December 15, 2006. Please direct inquiries about the position to **seamanm@duq.edu**.

Duquesne University was founded in 1878 by its sponsoring religious community, the Congregation of the Holy Spirit. Duquesne University is Catholic in mission and ecumenical in spirit. Motivated by its Catholic identity, Duquesne values equality of opportunity both as an educational institution and as an employer.

POSITIONS OPEN

FACULTY POSITION IN ENVIRONMENTAL STUDIES

Skidmore College seeks an interdisciplinary environmental Natural Scientist for a tenure-track position in our growing Environmental Studies (ES) Program. The successful candidate will be able to teach our interdisciplinary environmental studies foundation course, an upper-level environmental science methods course, and upper-level dedicated environmental science courses in the candidate's area of expertise. Establishment of a rigorous, interdisciplinary research program that involves undergraduates and complements our new Water Resources Initiative is expected. Expertise in geographic information systems is desirable. The successful candidate will also engage students in co-curricular activities that complement the academic mission of the ES program and contribute to our Institutional program to promote the public's understanding of science. The position rank is open, but qualified candidates should have completed their Ph.D. prior to June 2007. Skidmore is committed to increasing the diversity of the College community; scholars who will contribute to such diversity are especially encouraged to apply.

Skidmore College is a selective, four-year, private, nondenominational, coed liberal arts college with approximately 2,400 students. Excellent teaching and research facilities, and generous startup funds, are available. Please visit the program **website: http://www.skidmore.edu/academics/env/.**

Send a letter of application, curriculum vitae, three letters of reference, and a statement of teaching and research interests, including how these interests will be applied to work with undergraduates, to: **Karen Kellogg, Director of Environmental Studies, File #SI, Skidmore College, 815 North Broadway, Saratoga Springs, NY 12866.** Application review will begin December 1, 2006, and will continue until the position is filled.

Skidmore College is committed to being an inclusive campus community and, as an Equal Opportunity Employer, does not discriminate in its hiring or employment practices on the basis of gender, race or ethnicity, color, national origin, religion, age, disability, family or marital status, or sexual orientation.

ANIMAL PHYSIOLOGIST ASSISTANT PROFESSOR

A tenure-track opening for an Animal Physiologist is available in the Department of Biological Sciences at DePaul University starting September 2007. Successful candidate will be broadly trained in animal physiology with a strong commitment to undergraduate education. All subdisciplines and animal model systems will be considered. Ph.D. required; postdoctoral and previous teaching experience preferred. Teaching responsibilities to include some combination of: introductory biology with laboratory for nonmajors; co-teaching one quarter of three-quarter introductory biology sequence for majors; introductory and intermediate-level undergraduate course(s) in vertebrate physiology; and graduate/advanced undergraduate course in candidate's area of expertise. Startup funds are provided. The Department is housed in a modern biological and environmental sciences building with spacious and well-equipped teaching, research, and support facilities, including a 2,000 square foot state-of-the-art animal care facility. Review of applications will begin December 15, 2006, and will continue until position is filled. Please send: curriculum vitae; three letters of reference; statement of research interests; statement of educational philosophy and teaching interests; and general list of equipment and supply needs with cost estimates to: **Animal Physiology Search Committee, Department of Biological Sciences, DePaul University, 2325 N. Clifton Avenue, Chicago, IL 60614.** Additional inquiries to above address, or **fax: 773-325-7596; e-mail: jdean@depaul.edu.** *The Department of Biological Sciences seeks diversity in its faculty. We encourage applications from women, people of color, and the members of other historically underrepresented groups. DePaul University is committed to diversity and equality in education and employment.*

OHIO UNIVERSITY

The Ohio University Department of Biomedical Sciences, College of Osteopathic Medicine, invites applications for an 11-month tenure-track faculty position in medical microbiology at the **ASSISTANT PROFESSOR** level. A Ph.D. (or equivalent) and two to three years of postdoctoral training are required. The successful applicant is expected to develop an independent, externally funded research program and to participate in the delivery of pathogenic bacteriology in our integrated medical curriculum. Salary will be commensurate with experience and is accompanied by an excellent benefits package. To apply, curriculum vitae and statements of teaching and research interests must be submitted online at **website: http://www.ohiouniversityjobs.com/applicants/Central?quickFind=51967.** Also mail three representative reprints and arrange for the mailing of three letters of recommendation to: **Medical Microbiology Search Committee Chair, Department of Biomedical Sciences, Ohio University College of Osteopathic Medicine, 228 Irvine Hall, Athens, OH 45701.** Review of candidates will begin on December 1, 2006, but applications will be accepted until the position is filled. For questions about the position, contact **Peter Coschigano, Ph.D.** at **telephone: 740-593-9488** or **e-mail: coschiga@ohio.edu.** For more information about the Department please visit our **website: http://www.oucom.ohiou.edu/dbms/index.htm.** We seek a candidate with a commitment to working effectively with students, faculty, and staff from diverse backgrounds. *Ohio University, located in a picturesque college town in rural southeastern Ohio, is an Affirmative Action, Equal Opportunity Employer with a Dual-Career Network* ***(website: http://www.ohio.edu/dual).***

HYDROECOLOGIST
Washington State University
School of Earth and Environmental Sciences

The School of Earth and Environmental Science at Washington State University (WSU) seeks a tenure-track **ASSISTANT PROFESSOR** with expertise in hydroecology. The School will consider applicants from a variety of specialties that address questions linking water and ecological processes. Applicants must have a Ph.D. and provide evidence that they will develop an active, independently funded research program. Postdoctoral experience is strongly preferred. A commitment to teaching and student training is expected. Applicants should submit (1) a letter of application outlining teaching and research interests, (2) curriculum vitae, and (3) contact information for four professional references to: **Dr. Richard Gill, Hydroecology Search Chair, SEES, Washington State University, Pullman, WA 99164-2812 U.S.A.; e-mail: rgill@wsu.edu.** Review of Applications will begin December 1, 2006. *WSU is an Equal Employment Opportunity/Affirmative Action Employer.*

ACADEMIC GERIATRICIAN. Geriatrician Clinician-Educator or Clinician-Scientist position available at the University of California, San Diego (UCSD), in the Division of Geriatrics, Department of Medicine. Full-time or part-time clinical practice in geriatric medicine in an academic setting. Excellent opportunities for teaching, research, or pursuing other geriatrics-related academic interests. Salary/rank commensurate with candidate's experience and established UCSD salary scales. Superb benefits package. California medicine license/eligibility and Board certification/eligibility in internal medicine with Certificate of Added Qualifications in Geriatrics required. May include some weekend call. Reply to: **Laura L. Dugan, M.D., University of California, San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0746; telephone: 858-822-1058.** *Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITION, IMMUNOLOGY
San Jose State University, California

The Department of Biological Sciences at San Jose State University (SJSU) invites applications for a tenure-track position at the **ASSISTANT/ASSOCIATE PROFESSOR** level. Applicants must possess a Ph.D. in immunology. Preference will be given to applicants with postdoctoral experience. Duties will include coordinating and teaching an upper-division lecture and laboratory course in immunology, a graduate level immunologic techniques course, and coordinating the use of cell culture and flow cytometry facilities. Depending on the candidate's area of expertise, other possible assignments might include courses in flow cytometry, virology, and laboratories in microbiology or cell biology. Applicants must have a proven record or potential for excellence in teaching. The successful candidate must address the needs of a student population of great diversity, in age, cultural background, ethnicity, primary language, and academic preparation. Applicants must have research experience and publications in their discipline. The successful candidate must have the ability to establish an extramurally funded research program involving undergraduates and M.S. graduate students. Research collaborations with other Department faculty are encouraged. Opportunities for external collaboration include nearby biotechnology companies, Bay Area Universities, Moss Landing Marine Labs, and NASA Ames Research Center.

For consideration send a letter of application, curriculum vitae, official university graduate and undergraduate transcripts, a statement of teaching interests/philosophy and research interests, and at least three original letters of reference with contact information to the **Immunology Search Committee.** Please include job opening identification 12388 on all correspondence. Review of applications will commence on December 1, 2006, and continue until the position is filled. **Website: http://www.sjsu.edu/depts/Biology.** *SJSU is an Equal Opportunity/Affirmative Action Employer committed to the core values of inclusion, civility, and respect for each individual.*

Beloit College seeks a Ph.D. **MOLECULAR BIOLOGIST** who studies mechanisms of neurobiology, cell signaling, or structural biology for a tenure-track position beginning fall 2007, to teach an introductory laboratory course for majors and nonmajors, and intermediate and advanced laboratory courses in molecular biology. The successful candidate will also involve undergraduates in research and contribute to all-College programs (e.g., first-year seminars, interdisciplinary studies, writing program, and international education). An excellent opportunity to teach in a Department nationally known for student inquiry and collaborative learning. Apply to: **Ken Yasukawa, Beloit College, 700 College Street, Beloit, WI 53511** by 20 November 2006, for full consideration. Application information at **website: http://www.beloit.edu/~humanres/jobs/faculty.php.** *Beloit College is committed to the educational benefits of diversity, and urges all interested individuals to apply. Affirmative Action/Equal Employment Opportunity Employer.*

NEUROBIOLOGIST and VIROLOGIST. The Biology Department at Seattle University seeks candidates for two new tenure-track, faculty positions at the **ASSISTANT PROFESSOR** level. Clear evidence of a commitment to undergraduate teaching and research is essential. Teaching responsibilities will include courses related to each faculty member's interests and expertise at both the upper-division and lower-division levels. The new faculty members will be expected to develop active research programs involving undergraduates and to contribute to undergraduate advising. For a full description of each position and information about the application process, please see the **website: http://www.seattleu.edu/scieng/biology.** Contact: **Glenn Yasuda, Chair, Biology Department, Seattle University, e-mail: gyasuda@seattleu.edu** or **telephone: 206-296-5980.** *Seattle University is an Equal Opportunity Employer.*

POSITIONS OPEN

FACULTY POSITION
Skidaway Institute of Oceanography

We invite applications and nominations for one faculty position available 1 July 2007. This appointment is the first of several to be made over the next three years. While individuals from all disciplines of marine science may apply, we are particularly interested in the following areas of expertise:

Physical oceanography/hydrodynamics with expertise in measurement and modeling of ocean boundary processes. Specialties might include: coastal oceanography or meteorology, air/sea/land exchange, or benthic boundary layer processes. Preference will be given to candidates with proven abilities to integrate field observations and models to provide insights into process, interactions, and regulation of material fluxes.

Ecosystem health, with expertise in areas such as ecotoxicology and marine diseases. Investigators utilizing molecular tools in these areas are of particular interest.

Marine pelagic ecology, with interests in trophic interactions of metazooplankton or micronekton. Candidates with expertise in gelatinous zooplankton or the interface between unicellular and multicellular predators are particularly encouraged.

We seek faculty whose interests complement existing strengths (see **website: http://www.skio.usg.edu**) and who are interested in developing research programs in Georgia coastal environments such as the extensive salt marshes, estuaries, and continental shelf adjacent to the Institute. The candidate should be willing to participate in academic and research-based education and training programs. We anticipate that the appointment will be made at the **ASSISTANT PROFESSOR** level, but applications from more senior candidates may be considered in exceptional circumstances. Send curriculum vitae, statement of research interests and teaching experience, and contact information for at least three references to: **Oceanographer Search, Skidaway Institute of Oceanography, 10 Ocean Science Circle, Savannah, GA 31411.** Review of applications will begin on November 6, 2006, and will continue until the position is filled. *Equal Opportunity Employer/Affirmative Action Employer.*

FACULTY POSITION IN CANCER BIOLOGY
University of Cincinnati
Molecular Genetics, Biochemistry, and Microbiology

The Department of Molecular Genetics, Biochemistry and Microbiology, in affiliation with the University of Cincinnati Cancer Center, seeks to fill a tenure-track faculty position at any level **(ASSISTANT/ASSOCIATE/FULL PROFESSOR).** We seek candidates who have already established a highly competitive independent research program or who will be able to develop such a program. Research can be in any area of cancer biology, but we are particularly interested in basic research using molecular genetic and biochemical approaches to study signal transduction, oncogenes and tumor suppressor genes, mutation, DNA repair, genome stability, chromosome and chromatin structure, and cell cycle regulation.

The Department currently has 24 full-time faculty with interest in mutation, chromosome structure, cell differentiation and development, signal transduction, ion transport, microbiology, immunology, and structural biology (nuclear magnetic resonance and X-ray crystallography). Core facilities support production of transgenic and knockout mice, gene microarray analysis, proteomics, informatics and advanced microscopy (electron and confocal) and imaging. The Department has active graduate and postdoctoral programs.

For further information, please see **website: http://www.molgen.uc.edu/logic/.** Applicants should submit curriculum vitae, a brief description of research, and the names of three references to: **Jerry B. Lingrel, Ph.D., Professor and Chair, Department of Molecular Genetics, Biochemistry and Microbiology, P.O. Box 670524, Cincinnati, OH 45267-0524.**

The University of Mississippi

UNIVERSITY OF MISSISSIPPI
Molecular Systematics/ Phylogeography

The Department of Biology at the University of Mississippi invites applications for a **TENURE-TRACK ASSISTANT PROFESSORSHIP** in molecular systematics/phylogeography to start August 2007. To apply, please visit our online employment service at **website: http://jobs.olemiss.edu.** Also please see our **website: http://www.olemiss.edu/depts/biology/.**

The University of Mississippi has 14,016 full-time students on the Oxford Campus. The Department of Biology has 17 tenure-track faculty and seven instructors, 589 undergraduate majors, 13 M.S. students, and 15 Ph.D. students.

The town of Oxford, located in northern Mississippi near Memphis, has 14,497 residents. Oxford's high school students ranked in the 98th percentile for SAT/ACT scores. Oxford was cited by *The Washington Post* as "cosmopolitan, sophisticated, even trendy," and by *USA Today* as one of the top six college towns in the nation.

The University of Mississippi is an Equal Employment Opportunity/Affirmative Action/Title VI/Title IX/Section 504/ ADA/ADEA Employer.

FACULTY POSITION IN PLANT COMPARATIVE OR COMPUTATIONAL GENOMICS
University of Florida

The University of Florida, Department of Botany **(website: http://web.botany.ufl.edu/),** invites applications for a full-time, nine-month, tenure-track position in comparative or computational genomics at the level of **ASSISTANT PROFESSOR** to begin in August 2007. Candidates with expertise and research interests in development and application of tools to explore genomes, transcriptomes, and proteomes including interspecies comparisons and evolutionary genomics are desired. A strong commitment to both undergraduate and graduate teaching and training is required. This position will be affiliated with the Genetics Institute at the University of Florida **(website: http://www.ufgi.ufl.edu/)** and office/laboratory space is available in the new Cancer and Genetics Research Complex. The successful candidate is expected to maintain an active, high-level, and extramurally funded research program. Applicants should send curriculum vitae, brief statements of research interests and teaching philosophy, names of three references, and a selection of reprints (no more than five) to: **Comparative/Computational Genomics Search Committee, Department of Botany, University of Florida, 220 Bartram Hall, P. O. Box 118526, Gainesville, FL 32611-8526. E-mail: pdwill@botany.ufl.edu,**

Application materials should be received by December 15, 2006.

The University of Florida is an Equal Opportunity Institution.

ASSISTANT PROFESSOR: PLANT ECOLOGY

The Department of Botany at Oklahoma State University (OSU), **website: http://botany.okstate.edu,** seeks to fill a tenure-track Assistant Professor position in ecology. Successful candidates are expected to mentor students, develop extramurally funded experimental research on any aspect of plant ecology, and teach effectively in appropriate undergraduate and graduate courses. A Ph.D. degree, strong publication record, and postdoctoral experience are required. Position will remain open until filled; for full consideration, submit a PDF containing curriculum vitae, statements of research and teaching interests, and contact information for three references by 10 November 2006, to **e-mail: paula.shryock@okstate.edu.** *OSU is an Equal Opportunity, Affirmative Action Employer. Women and minorities are encouraged to apply.*

ASSISTANT/ASSOCIATE PROFESSOR
Immunology

St. Louis University, a Catholic Jesuit Institution dedicated to student learning, research, health care, and service offers a 12-month tenure-track faculty position at the **ASSISTANT or ASSOCIATE PROFESSOR** level in the Department of Molecular Microbiology and Immunology in the St. Louis University School of Medicine. The Department has active research programs in autoimmunity, bio-defense, molecular virology, vaccine development, viral pathogenesis, and viral vectors **(website: http://medschool.slu.edu/mmi).** We seek to expand our expertise in immunology, especially in the areas of autoimmunity and immune defenses to infectious disease and cancer. The candidate must have a D.V.M., M.D., Ph.D., or M.D./Ph.D. degree as well as postdoctoral experience. Potential candidates will be expected to develop and maintain a strong, externally funded research program and to teach graduate and medical students. Laboratory space in the new Biomedical Science Building will be available along with competitive startup funds and salary packages.

All applications must be made online at **website: http://jobs.slu.edu.** Additionally, applicants should send their curriculum vitae, a brief description of research, and names of three references interests to: **Dr. Harris Perlman, Associate Professor, Department of Molecular Microbiology and Immunology, St. Louis University School of Medicine, 1402 S. Grand Boulevard, St. Louis, MO 63104. E-mail: perlmanh@slu.edu.** *St. Louis University is an Affirmative Action, Equal Opportunity Employer, and encourages nominations and applications of women and minorities.*

DEPARTMENT OF PHYSIOLOGY
University of Utah School of Medicine

The Department of Physiology will undergo significant rebuilding, and several faculty will be recruited over the next few years. Applications will be considered in any area of physiology; however, the ideal candidate will have a research interest that is focused on renal, endocrine, or neural physiology with an emphasis on disease mechanisms. Applicants should hold a doctoral degree, have a strong research record, and be able to teach physiology to medical and graduate students. Candidates ranging from the level of **ASSISTANT PROFESSOR to PROFESSOR** will be considered. Ample startup packages and newly renovated laboratory space are available. Send curriculum vitae, a statement of teaching experience, and research background and interest, and the names of three potential references to:

Dr. F. Edward Dudek, Professor and Chair
c/o Ms. Vicki Skelton, Department of Physiology
University of Utah School of Medicine
420 Chipeta Way, Suite 1700
Salt Lake City, UT 84108-1297 U.S.A.
E-mail: vicki.skelton@hsc.utah.edu

The review of applications will begin immediately, and applications will be considered until the positions are filled. The University of Utah provides excellent benefits. Utah offers tremendous outdoor activities for all seasons, and Salt Lake City has outstanding cultural programs in a safe environment with a reasonable cost-of-living. *The University of Utah is an Affirmative Action/Equal Opportunity Employer that encourages applications from women and minorities, and seeks to provide equal access to its programs, services, and activities to people with disabilities.*

Adelphi University's Biology Department seeks a **FIELD ECOLOGIST** with a Ph.D., significant research accomplishments, and teaching potential for tenure-track **ASSISTANT PROFESSOR** position. Will develop fundable independent research program involving undergraduates and Master's students. May teach introductory biology, ecology, and/or biostatistics. To apply, go to **website: http://www.adelphi.edu/positions/faculty.** Application deadline: December 1, 2006. *We welcome applications from members of underrepresented groups. Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

MOLECULAR GENETICS

Washington State University Vancouver invites applications for a full-time tenure-track **ASSISTANT PROFESSOR** with research emphasis in molecular genetics in animal systems or other taxa that complement the strengths of existing faculty. Successful applicant will teach two courses per year, advise both graduate and undergraduate students, and establish a productive, externally funded research program. Excellence in research and instruction are the main criteria for selection. Minimum qualifications: Ph.D. in molecular biology, genetics, or related discipline by date of hire. Preferred candidates will demonstrate a commitment to working with diverse student and community populations. Washington State University Vancouver is located across the Columbia River from Portland, Oregon, and offers significant opportunities for research and an excellent quality of life. Additional information is available at **website: http://www.vancouver.wsu.edu/programs/sci/.**

Applicants should submit curriculum vitae, copies of two publications, summary of research accomplishments, statement of teaching philosophy and interests, and three letters of reference to: **Molecular Genetics Search, Washington State University Vancouver, 14204 N.E. Salmon Creek Avenue, Vancouver, WA 98686-9600.** Review of completed applications will begin on November 20, 2006.

Washington State University is an Equal Opportunity/Affirmative Action Educator and Employer. Members of groups historically underrepresented in science are strongly encouraged to apply.

TWO FACULTY POSITIONS IN THEORETICAL CHEMISTRY
University of California, Irvine

The Department of Chemistry at the University of California, Irvine (UCI), seeks to continue building on its existing breadth and strength in theoretical chemistry by making two new faculty appointments. Applications are invited from both **JUNIOR and SENIOR RANKS** in all areas of theoretical and computational chemistry, including, for example, methods development and application in the traditional areas of electronic structure, statistical mechanics, and dynamics, as well as interdisciplinary areas interfacing with biophysics, chemical biology, chemical engineering, materials science, chemical physics, nanotechnology, and bioinformatics. Candidates should have a visionary research program, and commitments to teaching and to the creation of a center of excellence in theoretical chemistry at UCI. A Ph.D. degree is required. To apply, electronically submit curriculum vitae, statements of research and teaching interests, and at least three letters of recommendation. Application instructions may be found at **website: http://ps.uci.edu/employment/apply.html.** Review of applications will begin November 15, 2006. *The University of California, Irvine, is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity. UC Irvine has an active Career Partners Program and has an ADVANCE Gender Equity Program.*

LANDSCAPE BIOLOGIST

The Department of Ecology, Evolution, and Environmental Biology (E3B) seeks to appoint a Landscape Biologist at the **ASSISTANT PROFESSOR** level. The successful candidate will be expected to establish a vigorous, externally funded research program complementing and augmenting existing strengths within E3B and related institutions **(website: http://www.columbia.edu/cu/e3b/job)** and to participate in undergraduate and graduate teaching. Candidates should send statements of research and teaching, curriculum vitae, and contacts for three or more references to: **E3B Search, Columbia University, 1200 Amsterdam Avenue, MC 5557, New York, NY 10027,** by November 20, 2006. A single PDF file of these materials should also be sent to **e-mail: eeeb-facsearch@columbia.edu.** Ph.D. required at time of appointment. *Applications from women and minorities are encouraged. Columbia University is an Equal Opportunity/Affirmative Action Employer.*

MAYO CLINIC
College of Medicine

POSTDOCTORAL POSITIONS
Transplantation Biology
Rochester, Minnesota, U.S.A.

Postdoctoral Positions are available in the Transplantation Biology Research Program. This program sponsors a wide range of basic investigation into such subjects as transplantation immunology, memory functions of T cells and B cells, stem cell biology, and endothelial cell biology. The faculty of the program includes Basic Scientists, Physicians, and Surgeons of diverse backgrounds who engage in collaborations to address problems of overarching importance. Inquiries should be directed to **Dr. Jeffrey L. Platt (e-mail: platt.jeffrey@mayo.edu)** and/or to **Dr. Marilia Cascalho (e-mail: cascalho.marilia@mayo.edu).**

Mayo Clinic College of Medicine is an Affirmative Action and Equal Opportunity Employer and Educator.

The Biology Department at the University of Arkansas at Little Rock invites applications for a **TENURE-TRACK ASSISTANT PROFESSOR** position to begin fall 2007. We seek a person with expertise in ecology/conservation biology. The successful candidate is expected to develop an extramurally funded research program that supports graduate and undergraduate research. Teaching duties include a Biology Department core course and courses in the candidate's specialty. Applicants must have a Ph.D. in the biological sciences; postdoctoral experience is expected. For more information about the University and the Department visit **website: http://www.ualr.edu.**

Little Rock's central location provides access to a diverse array of ecosystems, facilitating research at local, state, national, and global levels. Furthermore, because it is the capital, Little Rock provides numerous opportunities to interact with nearby, environmentally oriented government agencies and nongovernmental organizations.

To apply: submit letter of application and include the job number (215), curriculum vitae, statements of research interests and teaching philosophy, undergraduate and graduate transcripts, and three letters of reference. Review of applications will begin 13 November 2006, and continue until the position is filled. Send applications and have letters of reference forwarded via **e-mail: jmbush@ualr.edu** or by postal mail to: **Dr. John Bush, Faculty Search Committee, Biology FH-406, University of Arkansas at Little Rock, 2801 S. University Avenue, Little Rock, AR 72204-1099.**

The University of Arkansas at Little Rock is an Equal Employment, Affirmative Action Employer and actively seeks the candidacy of minorities, women, and persons with disabilities. Under Arkansas law, all applications are subject to disclosure. Persons hired must have proof of legal authority to work in the United States.

POSTDOCTORAL POSITION in biochemistry is available immediately for the investigation of a novel proteasome species, Blm 10-proteasomes. The main objective of the laboratory is to understand the mechanistic details of proteasome activation by Blm10 proteins, the identification of specific proteolytic targets of the complex and the analysis of its cellular function. Applicants should have a Ph.D. in a relevant science with a strong background in protein biochemistry and molecular biology. Prior experience in ubiquitin/proteasome research, in yeast genetics, and/or cell biological techniques is preferred. Please submit curriculum vitae, names of three references, and a letter describing research experience to: **Dr. Marion Schmidt, Department of Biochemistry, Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, Bronx, NY 10461. Telephone: 718-430-8868, e-mail: mschmidt@aecom.yu.edu.** *Equal Opportunity Employer.*

FACULTY POSITIONS IN MICROBIOLOGY AND IMMUNOLOGY
University of South Alabama

The Department of Microbiology and Immunology at the University of South Alabama College of Medicine is seeking applicants for three tenure-track positions at the rank of **ASSISTANT or ASSOCIATE PROFESSOR.** The Department is initiating an expansion in faculty positions and can offer the successful candidate substantial laboratory space and a competitive startup package. A Ph.D. and/or M.D. degree and postdoctoral experience are required. Successful candidates are expected to establish and maintain independent, extramurally funded research programs and to contribute to graduate and medical education. Candidates qualifying for an Associate Professor position must have a history of and current extramural funding. Candidates interested in bacterial or viral pathogenesis, host-pathogen interactions, and the immunology of infectious diseases including innate immunity are especially encouraged to apply, but outstanding candidates conducting state-of-the-art research in other areas of microbiology and immunology will be considered. Opportunities for interdisciplinary interactions with the Center for Lung Biology and other departments are available. An overview of the Department can be viewed at **website: http://www.southalabama.edu/microbiology/.** Please send curriculum vitae, a description of current and future research plans, and the names and contact information of three references to: **Dr. David O. Wood, Professor and Chair, Department of Microbiology and Immunology, College of Medicine, MSB 2096, University of South Alabama, Mobile, AL 36688-0002. E-mail: dowood@jaguar1.usouthal.edu.** Applications will be reviewed beginning October 15, 2006, and received until the positions are filled. *The University of South Alabama is an Equal Opportunity/Affirmative Action Employer.*

ARCHAEAL BIOLOGIST, UNIVERSITY OF NEBRASKA (UNL). The School of Biological Sciences invites applications for a tenure-track faculty position at the **ASSISTANT PROFESSOR** level with expertise in the area of archaeal biology. Candidates will be expected to develop a rigorous research program and assume teaching responsibilities in undergraduate courses in microbiology and evolutionary biology, and at the graduate level in areas emphasizing the genetics, genomics and biochemistry of archaea. A Ph.D. in the life sciences is required and postdoctoral experience is preferred.

To apply log on to **website: http://employment.unl.edu,** requisition number 060858 and complete the faculty/administrative information form and attach curriculum vitae; cover letter; statement of research interests,teaching interests, and philosophy; representative publications; names, addresses, and telephone numbers of three references. Arrange for three letters of reference to be sent by November 17, 2006, to: **Dr. Alan Kamil, School of Biological Sciences, University of Nebraska-Lincoln, 348 Manter Hall, Lincoln, NE 68588-0118.** Review of applications will begin November 17, 2006. The position will remain open until a suitable candidate is selected. *UNL is committed to a pluralistic campus community through Affirmative Action and Equal Opportunity, and is responsive to the needs of dual-career couples. We assure responsible accommodation under the Americans with Disabilities Act; for assistance contact* ***Dr. Alan Kamil*** *at* ***telephone: 402-472-6676.***

POSTDOCTORAL POSITIONS/DEPARTMENT OF MEDICINE, PULMONARY. Positions available for highly motivated individuals with Ph.D. or M.D. NIH-funded studies involve laboratory research in mouse models for lung cancer and role of tumor-stromal interactions in mediating progression. Two plus years of experience with mice, molecular biology, genomics, cell culture preferred. Please send curriculum vitae and two letters of reference to: **Charles A. Powell, M.D., Department of Medicine, 630 West 168th Street, P.O. Box 91, New York, NY 10032; e-mail: cap6@columbia.edu.** *Columbia University is an Equal Opportunity Employer.*

POSITIONS OPEN

DEPARTMENT OF ENVIRONMENTAL HEALTH SCIENCES
University of South Carolina

ASSISTANT/ASSOCIATE PROFESSOR, applied aquatic sciences. The University of South Carolina's Arnold School of Public Health is seeking qualified candidates for a full-time, nine-month tenure-track position at the rank of Assistant or Associate Professor in the Department of Environmental Health Sciences (ENHS). The successful candidate will have research/teaching interests in surface water quality linkages to land use, pathogen dynamics, urbanization, toxicant fate/effects, and/or HABs. Research strengths may include risk assessment or geographic information system-based modeling, environmental impact assessment, applied environmental genomics, and/or environmental disease processes. Strong evidence of the ability to develop an extramurally funded research program is desired. ENHS is located in the Public Health Research Center, a new 20,000 square-feet laboratory facility, and offers Master's and doctoral degrees in environmental quality, industrial hygiene, and hazardous materials management. Application deadline: November 11, 2006. Minimum qualifications: Ph.D. from an accredited University earned on or before 15 May 2007. Preferred qualifications: A qualification for this position is a record of excellence in externally funded research and scholarship, or strong evidence of the ability to develop such a research program. Postdoctoral experience is desired, but pre-doctoral candidates of high ability and potential are encouraged to apply. Special instructions to applicants: Application reviews will begin immediately and the position will remain open until filled. Applicants should apply online at **website: http://uscjobs.sc.edu,** requisition 042569, and also forward curriculum vitae, statement of professional goals in research and teaching, and names of three references (with mailing address, e-mail, and telephone number) to **Dr. Dwayne Porter, Search Committee Chair** at **e-mail: porter@sc.edu.** *The University of South Carolina is an Affirmative Action, Equal Opportunity Employer, and women and minorities are encouraged to apply.*

ASSISTANT PROFESSOR OF BIOLOGY
Tenure Track

The Biology Department at Millsaps College **(website: http://www.millsaps.edu)** seeks a broadly trained Ph.D. **BIOLOGIST** with a commitment to liberal arts education, combining outstanding classroom instruction with a passion for research that engages undergraduate students. Area of specialty is open and may include, but is not limited to: comparative physiology, herpetology, ornithology, entomology, but must be one that can be pursued effectively at the College's field station in southern Yucatan, Mexico **(website: http://www.kiuic.org/).** Spanish language a plus. The successful candidate will teach Introductory Cell Biology, General Zoology, upper-level courses in the specialty, and a course at the field station. Send curriculum vitae, statement of teaching philosophy, research interests, and names and full contact information for three references to: **Dr. Sarah L. Armstrong, Chair, Biology Search Committee, Millsaps College, 1701 N. State Street, Jackson, M.S. 39210. E-mail: armstsl@millsaps.edu.** Review of applications will begin November 15, 2006, and will continue until position is filled. *Minorities are especially encouraged to apply.*

NANOSCIENCE TECHNOLOGY CENTER GRADUATE FELLOWSHIPS

The NanoScience technology Center (NSTC) at the University of Central Florida is inviting exceptional graduate students seeking to pursue an education in the cutting-edge research field of nanoscience technology to apply for our four-year NSTC graduate fellowships. Awarded degrees will be in traditional disciplines (physics, chemistry, engineering, optics, computer and biomedical sciences), with a concentration in nanoscience. Further information and application forms are available on our **website: http://www.nanoscience.ucf.edu.**

POSITIONS OPEN

Benedictine University

TENURE-TRACK , FALL 2007 ASSISTANT PROFESSOR, BIOLOGICAL SCIENCES
Benedictine University

Teach freshman-level principles of biology lecture and laboratory sequence and advanced coursework in biomedical-related science; establish and participate in externally funded faculty/student research at the undergraduate level. Ph.D. required with research interest (pedagogical research included) involving undergraduate students; teaching and postdoctoral experience is preferred. *Must have legal authorization to work in the United States permanently.*

Application review begins December 1, 2006. Submit cover letter, curriculum vitae, graduate and undergraduate transcripts, statement of teaching and research interests, and three letters of recommendation (one addressing teaching effectiveness) to: **Dr. Allison Wilson, Search Committee Chair, Department of Biological Sciences, Benedictine University, 5700 College Road, Lisle, IL 60532. E-mail: mmosier@ben.edu. Fax: 630-829-6547.** *Equal Opportunity Employer.*

GENETICIST

St. Louis University, a Catholic, Jesuit Institution dedicated to student learning, research, health care, and service is seeking applicants for a tenure-track **ASSISTANT PROFESSOR** position in the Department of Biology. The successful candidate will work in genetics or related disciplines. Applicants should have a Ph.D., postdoctoral experience, and a record of research productivity. The successful candidate will be expected to develop an independent, extramurally funded research program and to contribute to our undergraduate and graduate curricula. Excellent facilities and a competitive startup package are provided, and opportunities are available to collaborate with researchers at the nearby Health Science Center, the Danforth Plant Science Center, Missouri Botanical Garden, St. Louis Zoo, and local Universities. Candidates whose research interests complement those of existing faculty in the Biology Department are encouraged to apply. All applications must be made online at **website: http://jobs.slu.edu** and must include curriculum vitae, and statements of both teaching and research goals. Three letters of recommendation should be sent to: **Dr. Richard L. Mayden, Department of Biology, St. Louis University, 3507 Laclede Avenue, St. Louis, MO 63103-2010.** Information about the Department and position is at **website: http://bio.slu.edu.** Review of applications will begin November 20, 2006, and will continue until suitable candidates are identified.

St. Louis University is an Affirmative Action, Equal Opportunity Employer, and encourages nominations and applications of women and minorities.

ASSISTANT PROFESSOR IN EVOLUTIONARY MORPHOLOGY

The Department of Zoology at the University of Florida seeks an **EVOLUTIONARY MORPHOLOGIST** broadly defined as one who studies morphology in an evolutionary context, from the functional, comparative, or developmental perspectives. Teaching requirement includes comparative/functional vertebrate morphology. Please submit curriculum vitae, a maximum of three reprints, and statements of research interests and teaching philosophy, both as hard copy and in PDF format on a CD, and have three letters of reference sent to: **Evolutionary Morphology Search Committee, Department of Zoology, P.O. Box 118525, University of Florida, Gainesville, FL 32611-8525.** Applications must be received by December 1, 2006. For more information, contact **e-mail: evomorphsearch@zoo.ufl.edu,** or visit **website: http://www.zoo.ufl.edu/evomorphsearch.** *Our Department is committed to diversity as a component of excellence. Women, minorities, and members of other underrepresented groups are particularly encouraged to apply. The University of Florida is an Equal Opportunity Institution.*

POSITIONS OPEN

PLANT GENETICIST AND VERTEBRATE PHYSIOLOGIST
TENURE-TRACK ASSISTANT PROFESSORS

The Department of Biology at Appalachian State University seeks to fill two tenure-track positions, one in vertebrate physiology and one in plant genetics, at the Assistant Professor rank. We seek teacher-scholars who will combine excellence in teaching at the undergraduate and graduate (Master's) levels with a strong externally funded research program. Postdoctoral experience is highly desirable.

Plant Geneticist will teach introductory botany, genetics, and courses in area of expertise. Research interests may include, but are not limited to, plant conservation, population, or developmental genetics. **(Search Chair: Dr. Gary Walker; e-mail: walkergl@appstate.edu.)**

Vertebrate Physiologist will teach introductory animal physiology and other undergraduate and graduate courses in area of expertise. Research expertise is open. **(Search Chair: Dr. Mark Venable; e-mail: venableme@appstate.edu.)**

Appalachian State, with an enrollment of over 15,000 students, is a highly ranked comprehensive University in the mountains of northwestern North Carolina and a member Institution of the 16-campus University of North Carolina system.

To apply, send a cover letter, curriculum vitae, statement of research interests, statement of teaching interests and philosophy, and contact information for at least three references (name, address, telephone, e-mail address) to: **Search Chair** (specify position), **Department of Biology, 572 Rivers Street, Appalachian State University, Boone, NC 28608.** Electronic applications accepted in PDF format only. Position will remain open until filled; review of applications begins October 31, 2006. For further details see **website: http://www.hrs.appstate.edu/employment/epa.htm.**

The University and Department **(website: http://www.biology.appstate.edu)** *are committed to increasing diversity and welcome applications from members of minority and underrepresented groups. Appalachian State University is an Affirmative Action/Equal Opportunity Employer.*

ILLINOIS NATURAL HISTORY SURVEY

ICHTHYOLOGIST, ASSISTANT PROFESSIONAL SCIENTIST. Conduct research on systematics (broadly defined) of freshwater fishes (including molecular and/or morphological phylogeny, population genetics, taxonomy, phylogeography, and/or conservation biology) with organismal and collections focus and applicability to Illinois and United States. Requires Ph.D. in ichthyology or related discipline. Responsibilities: develop vigorous, externally funded research program; publish research findings in scientific journals; curate Illinois Natural History Survey (INHS) ichthyology collection; work with state and federal agencies and University of Illinois. INHS is part of the Illinois Department of Natural Resources and an Affiliated Agency of the University of Illinois at Urbana-Champaign. For complete position description and application requirements visit our **website: http://www.inhs.uiuc.edu/opportunities.** Deadline January 4, 2007.

TIME FOR A CAREER CHANGE?

CPE Communications, a leader in pharmaceutical healthcare communications headquartered in Morristown, New Jersey, is looking for an enthusiastic, self-motivated **MEDICAL WRITER.** If you enjoy writing and learning about the pharmacologic management of disease, have excellent communication and presentation skills, and can adhere to deadlines and manage multiple projects, this job may be for you! Send inquiries, curriculum vitae, and salary requirement to **e-mail: hr@dpmadvert.com,** referring to code number MW10-06. Advanced degree required (Ph.D., Pharm.D, or M.D.). Dermatology, oncology, pharmacology, or immunology expertise is preferred. Must be willing to travel. CPE will train. Clinical experience a plus.

POSITIONS OPEN

FACULTY POSITION
Molecular Anthropology

Washington State University (WSU), Pullman, seeks a tenure-track **ASSISTANT PROFESSOR** for a new full-time position in molecular anthropology to be jointly appointed in the Department of Anthropology and the School of Biological Sciences beginning August 16, 2007. Required qualifications include a Ph.D. by July 1, 2007, in anthropology or a life science; an active research program commensurate with rank using molecular genetic approaches to address questions at the interface of biology and anthropology; and demonstrated expertise in one or more of the following areas: human genetics, ancient DNA, phylogenetics, phylogeography and population history, human evolution, zooarchaeology, or molecular evolution. The candidate will participate in a new WSU/University of Washington Integrative Graduate Education and Research Traineeship program entitled Model-based Approaches to Cultural and Biological Evolution; preferred qualifications include previous successes in interdisciplinary work in anthropology and biology and strengths in teaching and in evolutionary theory. Teaching expectations will depend on expertise but will likely include an undergraduate Introduction to Physical Anthropology in addition to undergraduate and/or graduate courses in areas of expertise in biology and anthropology. Full notice of vacancy at **website: http://libarts.wsu.edu/anthro/.**

To apply, send letter of application, two-page research statement, two-page teaching statement, curriculum vitae, and names and contact information for three references to: **Tim Kohler, Molecular Anthropologist Search Chair, Department of Anthropology, Washington State University, Pullman, WA 99164-4910.** All materials including letters must be received by 4 December 2006.

Equal Employment Opportunity/Affirmative Action/ADA.

The NCI-designated Cancer Research Center of the Burnham Institute for Medical Research seeks outstanding **INDEPENDENT INVESTIGATORS** at all levels of faculty. Areas of special interest are: cancer stem cells, tumor microenvironment, ubiquitin-mediated signaling, chromatin remodeling and epigenetics, proteomics, chemical genomics, and chemical glycomics. The new faculty members will join a highly interactive and multidisciplinary research environment that includes the Cancer Center, San Diego Center for Chemical Genomics, Center on Proteolytic Pathways, an NIH-funded Human Stem Cell Center, state-of-the-art research core facilities, and impending support of stem cell research by the state of California. Candidates should e-mail their application, preferably in PDF format, to **e-mail: ccrecruit@burnham.org** by December 1, 2006. The application should include curriculum vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three letters of reference sent by e-mail to **e-mail: ccrecruit@burnham.org** or regular mail to: **Cancer Center Recruit Committee, c/o Kristiina Vuori, M.D., Ph.D., NCI Cancer Center, Burnham Institute for Medical Research, 10901 North Torrey Pines Road, La Jolla, CA 92037.** *Equal Opportunity Employer/Affirmative Action.*

POSTDOCTORAL POSITION
University of California, Los Angeles

A Postdoctoral Position is available to work on projects in cancer and diabetes in a laboratory investigating growth factor biology. Expertise in cell/molecular biology techniques is required. A Ph.D. in a related subject and received within the last three years is required.

Interested persons, please submit your curriculum vitae, description of your scientific interests, and contact information with three references to: **Kuk-Wha Lee, M.D. Ph.D., Division of Pediatric Endocrinology, UCLA, 10833 Le Conte Avenue, MDCC 22-315, Los Angeles, CA 90095, e-mail: kukwhalee@mednet.ucla.edu.** *UCLA is an Equal Opportunity Employer.*

POSTDOCTORAL POSITION
Germline Stem Cells

Studies involve culture, differentiation, and gene activity of male germline stem cells. See *Proc. Natl. Acad. Sci.* **101**:16489, 2004 and *Proc. Natl. Acad. Sci.* **103:**9524, 2006. Send curriculum vitae, names of three references, and a letter describing research experience to: **R. L. Brinster, School of Veterinary Medicine, University of Pennsylvania. E-mail: cpope@vet.upenn.edu.**

BIOLOGY SEARCH 2006
Georgetown University

The Department of Biology, Georgetown University, invites applications to fill two tenure-track positions at the **ASSISTANT PROFESSOR** level beginning in August 2007.

We seek (1) a quantatatively oriented **ECOLOGIST** with research interests at the population, community, and/or ecosystem level; and (2) a **BIOINFORMATICIST** working in genomics or proteomics addressing fundamental hypotheses in molecular biology, genetics, or evolution. Preference is for candidates with a research emphasis that complements current faculty and interfaces with developing undergraduate programs in biology. Successful applicants will teach two courses per year, one in an area of expertise, and the other a gateway course in ecological analysis or introduction to bioinformatics, as well as establish grant-supported research programs involving both undergraduate and graduate students. Each candidate should have a Ph.D., relevant postdoctoral experience, and demonstrated ability as an Instructor.

Learn about our Department at **website: http://biology.georgetown.edu.**

Applications will include (1) curriculum vitae; (2) three letters from references able to address the applicant's research and teaching accomplishments; (3) a statement of the applicant's research interests and projected research program; and (4) a statement of the applicant's teaching philosophy and goals for a course in either ecological analysis or bioinformatics.

Applications should be submitted by December 15, 2006, to the appropriate Search Committee:

Ecologist Search or Bioinformatics Search
Department of Biology
P.O. Box 571229
Georgetown University
Washington, DC 20057-1229

Georgetown University is an Affirmative-Action, Equal-Opportunity Employer.

PLANT BIOLOGIST/DEVELOPMENT

The Department of Biology at Rhodes College **(website: http://www.rhodes.edu/biology)** offers a tenure-track **ASSISTANT PROFESSOR** appointment to begin August 2007. Candidates must have a Ph.D., a strong interest in undergraduate teaching, and the ability to maintain an active research program in a plant-based system involving undergraduate students. Preference will be given to those with postdoctoral experience and interest in interdisciplinary studies or teaching. Teaching responsibility is three-two and must include an upper-level course with laboratory in mechanisms of development. Full information on this and other positions is at **website: http://www.rhodes.edu.**

A letter of application, curriculum vitae, transcripts, research and teaching statements, and three letters of recommendation should be sent to: **Gary J. Lindquester, Ph.D., Chair, Department of Biology, Rhodes College, 2000 North Parkway, Memphis, TN 38112, e-mail: glindquester@rhodes.edu.**

Review of completed applications will begin on December 15, 2006. *Rhodes College is an Equal Opportunity Employer committed to diversity in the workforce and strongly encourages applications from women and minority candidates (see* ***website: http://www.rhodes.edu/about/376.asp).***

ASSISTANT PROFESSOR/SCIENCE EDUCATION
Department of Biology, Ball State University
Muncie, Indiana

Tenure-Track position available August 17, 2007. Responsibilities: teach undergraduate and graduate courses in elementary and secondary grades science methods and introductory biology for elementary education majors; promote student involvement in departmental academic activities. Minimum qualifications: earned doctorate in science education or related field with strong background in the life sciences earned by November 1, 2007; teacher certification or licensure; at least one year of full-time teaching experience at the elementary or secondary level; effective written and oral communication skills. Preferred qualifications: demonstrated teaching ability and publications and/or evidence of other scholarly activity; experience with and a commitment to one or more of the following: (a) working in professional development schools; (b) using technology as a tool for teaching and learning; (c) participating in interdisciplinary collaborations.

Send letter of application, curriculum vitae, documentation of scholarly activity, transcripts, and three letters of reference to: **Dr. Melissa Mitchell, Chair, Science Education Search Committee, Department of Biology, Ball State University, Muncie, IN 47306. (Website: http://www.bsu.edu)** Deadline for applications is November 14, 2006.

Ball State University is an Equal Opportunity, Affirmative Action Employer and is strongly and actively committed to diversity within its community.

PLANT FUNCTIONAL GENOMICIST

The University of Georgia has an opening at the **ASSISTANT PROFESSOR** level for a Plant Functional Genomicist. Those who use cutting-edge genome-wide technologies to address issues in genetics and evolution are particularly encouraged to apply. The successful candidate is expected to develop a vigorous externally funded research program and to interact with the existing strong plant groups at the University of Georgia. Further information about those working on plants can be found at the websites of the Departments of Plant Biology **(website: http://www.plantbiology.uga.edu)** and of the Plant Center **(website: http://www.plantcenter.uga.edu/).**

To apply, candidates should (1) combine a cover letter, curriculum vitae, short statements of research interests and teaching philosophy into a single PDF file; (2) three reprints of research papers should also be combined into a separate PDF file. These two files should then be submitted online at **website: http://www.plantbio.uga.edu/pfg/positions.html.** (3) Candidates should arrange to have four letters of recommendation submitted to the same website, or sent to: **Chairperson, Plant Functional Genomicist Search Committee, Plant Biology Department, Miller Plant Sciences Building, University of Georgia, Athens, GA 30602-7271.**

Applications received by 1 December 2006, are assured full consideration. *The Franklin College of Arts and Sciences is committed to increasing the diversity of its faculty and strongly encourages applications from individuals in underrepresented groups. University of Georgia,Athens, is an Equal Opportunity Employer.*

POSTDOCTORAL FELLOW

(26UC3422) The University of Cincinnati (UC), College of Medicine, Genome Science is accepting applications for a Postdoctoral Fellow to perform research in molecular biology, biochemistry, and cell culture in animal models. Minimum qualifications include a Ph.D. with experience in molecular biology and with zebra fish. Pay is commensurate with experience. For additional information and to apply for position 26UC3422, please see **website: http://www.jobsatuc.com.** *UC is an Affirmative Action/Equal Opportunity Employer.*

CONFERENCE CENTRE
HINXTON CAMBRIDGE UK

wellcome trust

WELLCOME TRUST SCIENTIFIC CONFERENCE

ANIMAL HEALTH RESEARCH: RECENT DEVELOPMENTS AND FUTURE DIRECTIONS

24–26 January 2007

Wellcome Trust Conference Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK

Background

The health of livestock is critically related to human health in developing countries and is a neglected research field. This meeting, hosted by the Wellcome Trust and sponsored by *Science* magazine, will review the current challenges in this area and will include issues around the translation of research into policy and practice.

As well as plenary sessions, the meeting will include workshops and poster sessions. For conference registration details visit:

www.wellcome.ac.uk/conferences

Please note there are a limited number of places for this meeting, priority will be given to scientists from developing countries.

Speakers include:

Professor Lonnie King, CDC/CCIID/NCID
Professor Don McManus, Queensland Institute of Medical Research
Professor Guy Palmer, Washington State University of Medical Research
Dr Jim Kaufman, Institute of Animal Health
Professor Louise Nel, University of Pretoria
Dr Mark Rweyemamu, Avis College
Professor Mark Woolhouse, University of Edinburgh
Professor Matthew Baylis, University of Liverpool
Professor Tom Barrett, Institute of Animal Health
Dr Jakob Zinsstag, Swiss Tropical Institute

The Wellcome Trust is a registered charity, no. 210183.

Science AAAS

UNCF • MERCK SCIENCE INITIATIVE

"A mind is a terrible thing to waste"

MERCK

UNDERGRADUATE SCIENCE RESEARCH SCHOLARSHIP AWARDS

- 15 Awards Annually
- Scholarships up to $25,000
- Two Summer Internships at a Merck Research Facility

An applicant must:

- Be a full-time student at any four-year college or university
- Have junior year academic status
- Major in a life or physical science (first professional degrees excluded)
- Have a minimum cumulative GPA of 3.3 (4.0 point scale)

GRADUATE SCIENCE RESEARCH DISSERTATION FELLOWSHIPS

- 12 Fellowships Annually
- Fellowship Stipends up to $42,000
- Department Grants of $10,000
- Support for 12-24 months

An applicant must:

- Be enrolled full-time in a Ph.D. or equivalent doctoral program in a biomedical life or physical science
- Be engaged in and within 1-3 years of completing dissertation research

POSTDOCTORAL SCIENCE RESEARCH FELLOWSHIPS

- 10 Fellowships Annually
- Fellowship Stipends up to $70,000
- Department Grants of $15,000
- Support for 12-24 months

An applicant must:

- Hold a Ph.D. or equivalent degree in a biomedical life or physical science
- Be appointed as a new or continuing postdoctoral fellow by the end of 2007 at an academic or non-academic research institution (private industrial laboratories are excluded)

Applicants must be African American (Black), U.S. citizens or permanent residents, and attending an institution in the U.S.A. Applications must be submitted online at www.uncf.org/merck/ or postmarked by December 15, 2006

For more information, please contact your department chairperson or Jerry L. Bryant, Ph.D., at the **United Negro College Fund**, Inc., 8260 Willow Oaks Corporate Drive, P.O. Box 10444, Fairfax, VA 22031-4511, by fax (703) 205-3574, by e-mail at ***uncfmerck@uncf.org***.

POSITIONS OPEN

DEVELOPMENTAL CELL BIOLOGIST AT MIDDLEBURY COLLEGE. The Department of Biology at Middlebury College invites applications for a tenure-track appointment at the rank of **ASSISTANT PROFESSOR** (Ph.D.) in developmental cell biology, beginning in September 2007. Applicants should have a demonstrated commitment to excellence in both teaching and research. Teaching responsibilities will include core instruction in biology and molecular biology and biochemistry, as well as an upper level course in developmental biology, and other courses in the applicant's field that can serve to strengthen and broaden our existing course offerings in cellular and molecular biology. The successful candidate will also be expected to participate in an interdisciplinary program in molecular biology and biochemistry, and to establish an active research program that will attract undergraduates. Applications including curriculum vitae, statements of teaching and research interests, samples of scholarly work, and three current letters of recommendation (at least one of which speaks to teaching ability), should be sent to: **Dr. Jeremy Ward, Developmental Cell Biology Search Committee, Department of Biology, Middlebury College, Middlebury, VT 05753.** See **website: http://www.middlebury.edu/depts/bio/** for more details. The review of completed applications will begin on November 17, 2006. *Middlebury College is an Equal Opportunity Employer committed to recruiting a diverse faculty to complement the increasing diversity of our student body.*

EUKARYOTIC MOLECULAR MICROBIOLOGIST ASSISTANT PROFESSOR

The Department of Biological Sciences, California State University, Los Angeles, seeks to fill a Tenure-Track position in eukaryotic molecular microbiology beginning fall 2007. Preference will be given to individuals studying medically relevant protozoa or fungi. Ph.D. in microbiology or related field or M.D. degree and specialized training in microbiology is required. A minimum of two years of relevant postdoctoral experience is required. The selected candidate will be expected to teach undergraduate and graduate microbiology courses, participate in our programmatic development, and develop a productive, externally funded basic or applied research program involving undergraduate and Master's students. The selected candidate is also expected to participate in University service and to provide academic advisement to students. Submit curriculum vitae, a statement of teaching philosophy, a research plan, and three letters of reference to: **Dr. Nancy McQueen, Search Committee Chair, Department of Biological Sciences, California State University, Los Angeles, 5151 State University Drive, Los Angeles, CA 90032 (e-mail: nmcquee@calstatela.edu).** Review of completed applications will begin November 6, 2006. Position will remain open until filled. *Equal Opportunity/Title IX/ADA Employer. Qualified women and minorities are encouraged to apply.*

Two **POSTDOCTORAL POSITIONS** at University of Alabama at Birmingham: (1) Microbiology/pathogenicity: The outer membrane of *Mycobacterium tuberculosis (Mtb)* is unique and hosts proteins with novel structures (*Science* **303:** 1189, 2004) and functions. These proteins are likely to be important for nutrient uptake and host-pathogen interactions. The goal of this NIH-funded project is to identify *Mtb* OMPs by a proteomic approach. (2) Biochemistry/nanotechnology: The goal of this NIH-funded project is to develop the mycobacterial porin *Mycobacterium smegmatis* (*Science* **303:** 1189, 2004) as the central part of a revolutionary sequencing technology. Experience with protein purification by high performance liquid chromatography is required. A background in electrophysiology is beneficial.

Our new laboratory, the Department of Microbiology, and the University of Alabama at Birmingham provide an outstanding research environment. Please send your curriculum vitae to **Michael Niederweis** at **e-mail: mnieder@uab.edu.**

POSITIONS OPEN

INSTITUT PASTEUR

POSTDOCTORAL FELLOWSHIPS
Institut Pasteur, Paris, France

Founded in 1887 by Louis Pasteur and located in the heart of Paris, the Institut Pasteur is a world-renowned private research organization. The Pasteur Foundation is seeking outstanding Fellowship Applicants. Candidates may apply to any laboratory within 10 departments: cell biology and infection; developmental biology; genomes and genetics; immunology; infection and epidemiology; microbiology; neuroscience; parasitology and mycology; structural biology and chemistry; and virology. See website for details.

Fellowships are $60,000 per year for three years ($45,000 stipend plus $15,000). *U.S. citizenship required.* Deadline: February 2, 2007.

E-mail: pasteurus@aol.com.

Website: http://www.pasteurfoundation.org.

BIOLOGY FELLOWSHIP

The Biology Department of Rhodes College offers a two-year **POSTDOCTORAL RESEARCH/TEACHING FELLOWSHIP** to begin August 2007. The position is an opportunity to develop teaching skills and engage in research with a faculty sponsor, and includes annual research support. See **website: http://www.rhodes.edu/biology** for descriptions of research interests of faculty open for collaboration. Applicants must have a Ph.D., a strong interest in undergraduate teaching, and a commitment to research. Complete information on this and other positions is at **website: http://www.rhodes.edu.**

A letter of application, curriculum vitae, transcripts, a statement of teaching goals/philosophy and how one's research program will integrate into the current biology program, and three letters of recommendation should be sent to: **Dr. Jay Blundon, Department of Biology, Rhodes College, 2000 N. Parkway, Memphis, TN 38112, e-mail: blundon@rhodes.edu.**

Review of completed applications will begin December 15, 2006. *Rhodes College is an Equal Opportunity Employer committed to diversity in the workforce (see* ***website: http://www.rhodes.edu/about/376.asp).***

PRINCIPAL INVESTIGATOR AT CENTER FOR DRUG DESIGN

The Center for Drug Design at the University of Minnesota invites applications for a Principal Investigator in virology and cell biology. The successful candidate will have a Ph.D., postdoctoral experience, strong record of research accomplishments and publications, and have potential to build an independent research program relevant to improving disease control. Experience with virus attachment and entry, transcription, assembly, modulation of host signaling, antigenic structure and molecular recognition is highly desired. Development of methods (replicon systems, enzyme inhibition, et cetera) for evaluation of new antiviral agents is expected. Competitive salary, startup package, and new laboratory space are available. Submit a letter of application, curriculum vitae, a statement of research interests containing research plans, and three names of references to: **Professor Krzysztof W. Pankiewicz, Senior Associate Director, Center for Drug Design, 7-215 PWB MMC 204, 516 Delaware Street S.E., Minneapolis, MN 55455; e-mail: panki001@umn.edu.**

The University of Minnesota is an Equal Opportunity Employer.

POSITIONS OPEN

I am looking for a very motivated **POSTDOCTORAL FELLOW** to join a well-established project to study a role of serine-threonine kinase PAK1 in signal transduction. A Ph.D. in cell biology/biochemistry/molecular biology and strong experience in biochemical methods are required, experience establishing stable cell lines would be outstanding. Publication record in English language, peer-reviewed journals is essential. Verbal and written communication skills in English are necessary. Review will begin on November 1, 2006, and the position will remain open until filled.

Send cover letter and resume with the names of three references to: **Maria Diakonova, Department of Biological Sciences, University of Toledo, 2801 Bancroft Street-MS601, Toledo, OH 43606. E-mail: mdiakon@utnet.utoledo.edu.**

The University of Toledo is an Affirmative Action/ Equal Opportunity Employer and Educator, Minorities/Females/Persons with Disabilities/Veterans.

PROFESSOR/PROGRAM DIRECTOR
Biology

The University of South Carolina (USC), Beaufort, invites applications for a tenure-track position in biology to serve as Program Director. Salary and rank commensurate with education and experience. Teaching requirements: courses in physiology; cell and molecular biology; and participation in introductory sequence. Research areas: cell, environmental, or other areas examining molecular/biochemical aspects of physiology. Ability to involve undergraduates in research is considered essential. Review of applications will begin November 2006. For additional information contact **Dr. Joseph L. Staton, telephone 843-208-8105.**

For details go to **website: http://www.uscb.edu/Employment_Opportunities.**

USC Beaufort is an Equal Opportunity Employer.

AWARDS

2007 STAGLIN FAMILY MUSIC FESTIVAL
NARSAD Schizophrenia Research Award

National Alliance for Reseach on Schizophrenia and Depression (NARSAD) announces a research grant competition for $250,000 for one investigator with doctoral degree and postdoctoral training applicable to schizophrenia, at **ASSISTANT or ASSOCIATE PROFESSOR** level, age 45 or younger. Nomination from Dean or Chair of employing University required. Due December 4, 2006, start date September 15, 2007. **Website: http://www.narsad.org** or **telephone: 516-829-5576.**

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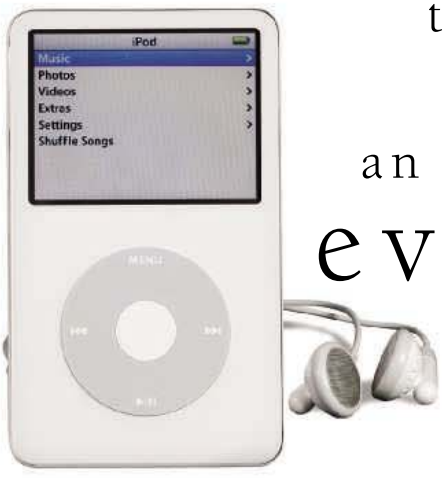

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